



Europäisches Patentamt  
European Patent Office  
Office européen des brevets

(11) Publication number:

**0 226 304  
A1**

(12)

# EUROPEAN PATENT APPLICATION

(21) Application number: 86308321.8

(51) Int. Cl.<sup>4</sup>: **A61K 31/40**, **A61K 31/43**,  
//(**A61K31/40,31:195**),(**A61K31/-  
43,31:195**)

(22) Date of filing: 24.10.86

(30) Priority: 24.10.85 JP 238283/85  
10.04.86 JP 81218/86

(43) Date of publication of application:  
24.06.87 Bulletin 87/26

(84) Designated Contracting States:  
**AT BE CH DE ES FR GB IT LI LU NL SE**

(71) Applicant: **SANKYO COMPANY LIMITED**  
**No. 1-6, 3-chome Nihonbashi Honcho**  
**Chuo-ku**  
**Tokyo(JP)**

(72) Inventor: **Shiokari, Takashi c/o Product**  
**Development Labs.**  
**Sankyo Co. Ltd. 2-58, 1-chome**  
**Hiromachi Shinagawa-ku Tokyo(JP)**  
Inventor: **Ueda, Selgo c/o Product**  
**Development Labs.**  
**Sankyo Co. Ltd. 2-58, 1-chome**  
**Hiromachi Shinagawa-ku Tokyo(JP)**  
Inventor: **Iwata, Masayuki c/o Product**  
**Development Labs.**  
**Sankyo Co. Ltd. 2-58, 1-chome**  
**Hiromachi Shinagawa-ku Tokyo(JP)**  
Inventor: **Kawahara, Yukinori c/o Product**  
**Development Labs.**  
**Sankyo Co. Ltd. 2-58, 1-chome**  
**Hiromachi Shinagawa-ku Tokyo(JP)**

(74) Representative: **Gibson, Christian John Robert**  
**et al**  
**MARKS & CLERK 57/60 Lincoln's Inn Fields**  
**London WC2A 3LS(GB)**

**EP 0 226 304 A1**

(54) Composition containing a penem or carbapenem antibiotic and the use of the same.

(57) Administration of an N-acylated amino acid in association with a penem or carbapenem antibiotic relieves or eliminates the renal problems associated with administration of the antibiotic alone. The amino acid derivative and antibiotic may be formulated together as a composition or administered separately, either simultaneously or sequentially. The composition may be prepared by simple mixing.

**COMPOSITION CONTAINING A PENEM OR CARBAPENEM ANTIBIOTIC AND THE USE OF THE SAME**

The present invention relates to a novel composition comprising a penem or carbapenem antibiotic in association with an amino acid derivative. The invention also provides a method of treating bacterial infections by administering to the patient, simultaneously or sequentially, a penem or carbapenem antibiotic and at least one N-acylated amino acid.

5 The class of compounds known as "penem and carbapenem antibiotics" is, of course, very well known and is potentially of great value for the treatment of bacterial infections. Although, as a group, these penem and carbapenem antibiotics exhibit excellent anti-bacterial activity and a variety of other properties which render them highly suitable for pharmaceutical use, they do have a number of disadvantages. One of the problems of these antibiotics is that, in general, they exhibit a degree of renal toxicity, and some degree of  
10 kidney damage is a frequent side effect of their use; accordingly, such penem and carbapenem antibiotics should not be used for the treatment of patients with actual or suspected impaired renal function. As a result, the penem and carbapenem antibiotics cannot be used for many patients for whom otherwise they would be the antibiotic of choice. The problem of renal toxicity is particularly acute when the antibiotics are administered by intravenous or intramuscular injection in a high dose.

15 We have now surprisingly discovered that the concurrent, or effectively concurrent, administration, with the penem or carbapenem antibiotic, of one or more of a certain class of acylated amino acid derivatives significantly reduces this renal toxicity.

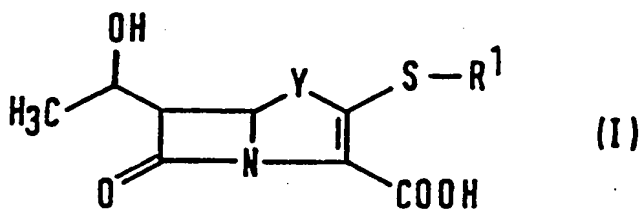
EP Publication No. 7614 discloses the use of a dipeptidase inhibitor in association with antibiotics similar to those to which the present invention relates. However, the dipeptidase inhibitors employed are  
20 structurally different from the amino acid derivatives of the present invention and are employed for a totally different purpose. The amino acid derivatives of the present invention and are employed for a totally different purpose. The amino acid derivatives employed in the present invention possess little or no dipeptidase inhibitory activity.

Accordingly, in one aspect, the present invention provides a composition comprising:

- 25 (a) a penem or carbapenem antibiotic; and  
(b) a pharmaceutically acceptable N-acylated derivative of an amino acid wherein the amino group and the carboxylic acid group are attached to a saturated aliphatic carbon chain or carbon atom, or a salt thereof, provided that the amino acid is not ornithine, lysine, phenylalanine or phenylglycine alone.

EP Application No. 85307427.6 discloses such a composition where the amino acid is ornithine, lysine,  
30 phenylalanine or phenylglycine.

There is no particular limitation on the nature of the penem or carbapenem antibiotic to which the present invention can be applied and it is believed that the beneficial effects of the concurrent administration of the N-acylated amino acid derivative will be achieved regardless of the particular antibiotic chosen. However, the penem and carbapenem antibiotics which are currently of most actual or potential interest  
35 may be represented by the general formula (I):



in which:

Y represents a sulphur atom, a methylene group or a methylene group having 1 or 2 methyl and/or methoxy substituents; and

50 R<sup>1</sup> represents a C<sub>1</sub>-C<sub>4</sub> alkyl group, a C<sub>1</sub>-C<sub>4</sub> alkyl group having at least one of substituents (i) or a heterocyclic group having from 4 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms where said heterocyclic group is unsubstituted or has at least one of substituents (ii);  
substituents (i):

halogen atoms, amino groups, amino groups having at least one of substituents (iii), C<sub>1</sub>-C<sub>4</sub> alkylideneamino

groups, C<sub>1</sub>-C<sub>6</sub> aminoalkylideneamino groups, amidino groups, amidino groups having from 1 to 3 of substituents (iii), heterocyclic groups having from 4 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms wherein said heterocyclic group is unsubstituted or has at least one of substituents (ii), imino groups, cyano groups, carbamoyl groups and carbamoyl groups having at least one C<sub>1</sub>-C<sub>6</sub> alkyl and/or C<sub>1</sub>-C<sub>6</sub> alkoxy substituent;

substituents (ii):

C<sub>1</sub>-C<sub>6</sub> alkanimidoyl groups, C<sub>1</sub>-C<sub>6</sub> alkyl groups, alkoxyalkyl groups where the alkoxy and alkyl parts are each C<sub>1</sub>-C<sub>6</sub>, carbamoyl groups, carbamoyl groups having at least one C<sub>1</sub>-C<sub>6</sub> alkyl and/or C<sub>1</sub>-C<sub>6</sub> alkoxy substituent, C<sub>1</sub>-C<sub>6</sub> haloalkyl groups, heterocyclic acylimidoyl groups where the heterocyclic part has from 5 to 9 ring atoms of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur hetero-atoms, amidino groups, amidino groups having from 1 to 3 of substituents (iii), imino groups, oxygen atoms, C<sub>1</sub>-C<sub>6</sub> alkanoyl groups, C<sub>1</sub>-C<sub>6</sub> alkanesulphonyl groups, C<sub>1</sub>-C<sub>6</sub> alkanesulphinyl groups, hydroximino groups, C<sub>1</sub>-C<sub>6</sub> alkoximino groups, carbamoyloxy groups, carbamoyloxy groups having at least one C<sub>1</sub>-C<sub>6</sub> alkyl and/or C<sub>1</sub>-C<sub>6</sub> alkoxy substituent, carbamoyloxyalkyl groups where the alkyl part is C<sub>1</sub>-C<sub>6</sub> and the carbamoyl part is unsubstituted or has at least one C<sub>1</sub>-C<sub>6</sub> alkyl and/or C<sub>1</sub>-C<sub>6</sub> alkoxy substituent and C<sub>1</sub>-C<sub>6</sub> iminoalkyl groups;

substituents (iii):

C<sub>1</sub>-C<sub>6</sub> alkyl groups, C<sub>2</sub>-C<sub>6</sub> alkenyl groups, C<sub>2</sub>-C<sub>6</sub> alkynyl groups, oxygen atoms and said alkyl, alkenyl and alkynyl groups having at least one substituent selected from halogen atoms, carbamoyloxy groups and carbamoyloxy groups having at least one C<sub>1</sub>-C<sub>6</sub> alkyl and/or C<sub>1</sub>-C<sub>6</sub> alkoxy substituent.

Preferably Y represents a sulphur atom, a methylene group, or the group CH<sub>2</sub>-CH<, CH<sub>2</sub>O-CH< or - (CH<sub>2</sub>)<sub>2</sub>C<.

Preferred examples of groups which may be represented by R<sup>1</sup> include the ethyl, 2-fluoroethyl, 2-(aminomethyleneamino)ethyl, N<sup>1</sup>,N<sup>1</sup>-dimethylamidinomethyl, N<sup>1</sup>,N<sup>1</sup>,N<sup>2</sup>-trimethylamidinomethyl, 3-pyrrolidinyl, 1-formimidoyl-3-pyrrolidinyl, 1-acetimidoyl-3-pyrrolidinyl, 1-propionimidoyl-3-pyrrolidinyl, 2-methyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 2-methoxymethyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 3-azetidiny, 1-acetimidoyl-3-azetidiny, N<sup>1</sup>-methyl-N<sup>1</sup>-(2-propynyl)amidinomethyl, N<sup>1</sup>-(2-fluoroethyl)-N<sup>1</sup>-methylamidinomethyl, N<sup>1</sup>-(3-fluoropropyl)-N<sup>1</sup>-methylamidinomethyl, N<sup>1</sup>-methyl-N<sup>1</sup>-(2,2,2-trifluoroethyl)amidinomethyl, 1-(3-azetidiny)ethyl, 1-(1-acetimidoyl-3-azetidiny)ethyl, 1,4,5,6-tetrahydro-2-pyrimidinylmethyl, 1-(4,5-dihydro-2-thiazolyl)ethyl, 5-carbamoyl-3-pyrrolidinyl, 1-acetimidoyl-5-carbamoyl-3-pyrrolidinyl, 2-chloromethyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 1-butyrimidoyl-3-pyrrolidinyl, 1-nicotinimoyl-3-pyrrolidinyl, N<sup>1</sup>,N<sup>1</sup>-diallylamidinomethyl, N<sup>1</sup>-methyl-N<sup>1</sup>-(2-propynyl)amidino, N<sup>1</sup>-(2-fluoroethyl)-N<sup>1</sup>-methylamidino, N<sup>1</sup>-(3-fluoropropyl)-N<sup>1</sup>-methylamidino, N<sup>1</sup>-methyl-N<sup>1</sup>-(2,2,2-trifluoroethyl)amidino, N<sup>1</sup>-allyl-N<sup>1</sup>-methylamidinomethyl, cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 2-cyano-1-methylethyl, 2-aminoethyl, 1-carbamoylethyl, 2-(1-aminoethylideneamino)ethyl, 1-amidino-3-pyrrolidinyl, 2-methyl-1,3-diazabicyclo[3.3.0]oct-2-en-7-yl, 2-methoxymethyl-1,3-diazabicyclo[3.3.0]oct-2-en-7-yl, 5-imino-2-pyrrolidinyl, 2-imino-5-piperidinyl, 1-acetimidoyl-5-methylcarbamoyl-3-pyrrolidinyl, 1-acetimidoyl-5-methoxycarbamoyl-3-pyrrolidinyl, 2-imino-2-(S-oxothiomorpholino)ethyl, 2-imino-2-(1,1-dioxo-1,3-thiazolidin-3-yl)ethyl, 2-imino-2-(S,S-dioxothiomorpholino)ethyl, 2-imino-2-(3,5-dioxo-1-piperazinyl)ethyl, 2-imino-2-(4-methyl-3,5-dioxo-1-piperazinyl)ethyl, 2-imino-2-(3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-methyl-3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-acetyl-3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-methanesulphonyl-3-oxo-1-piperazinyl)ethyl, N<sup>1</sup>-(2-carbamoyloxyethyl)-N<sup>1</sup>-methylamidinomethyl, 2-(3-hydroximino-1-pyrrolidinyl)-2-iminoethyl, 2-imino-2-(3-methoximino-1-pyrrolidinyl)ethyl, 2-(4-hydroximino-piperidino)-2-iminoethyl, 2-imino-2-(4-methoximino-piperidino)ethyl, 2-(3-carbamoyloxy-1-pyrrolidinyl)-2-iminoethyl, 2-imino-2-(3-oxo-1-piperazinyl)ethyl, 2-(3-carbamoylpiperidino)-2-iminoethyl, 2-(3-carbamoyloxypiperidino)-2-iminoethyl, 2-(2-carbamoyloxy-1-pyrrolidinyl)-2-iminoethyl, 2-(2-carbamoyloxymethyl-1-pyrrolidinyl)-2-iminoethyl, 2-(4-carbamoyloxypiperidino)-2-iminoethyl, 2-(4-formyl-1-piperazinyl)-2-iminoethyl, 2-(4-acetyl-1-piperazinyl)-2-iminoethyl, 1-formyl-3-azetidiny, 1-iminomethyl-3-azetidiny, 1-methyl-4-piperidyl, 1-acetimidoyl-4-piperidyl and 1-acetyl-3-pyrrolidinyl groups.

The invention may also be applied to pharmaceutically acceptable salts and esters of such antibiotics, such as are well known in the art.

Specific examples of compounds of formula (I) which may be employed in the present invention are those in which R<sup>1</sup> and Y are as defined below:

5

10

15

20

25

30

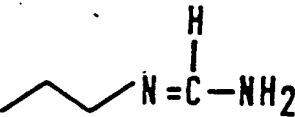
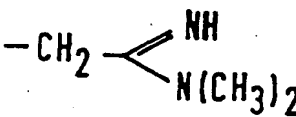
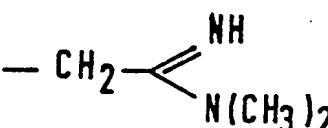
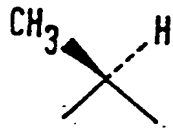
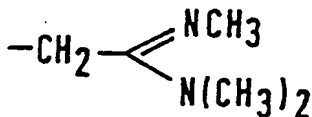
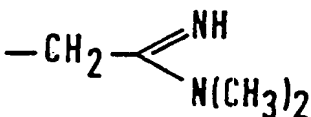
35

40

45

50

55

Comp. No.	R <sup>1</sup>	Y
1.		CH <sub>2</sub>
2.		CH <sub>2</sub>
3.		
4.		CH <sub>2</sub>
5.		S

5

10

15

20

25

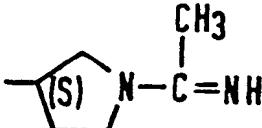
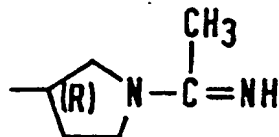
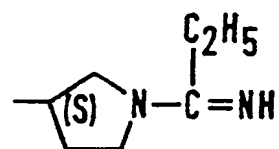
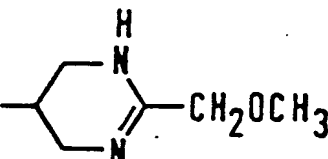
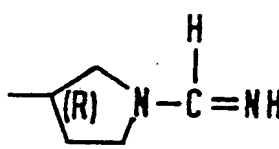
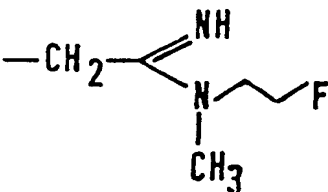
30

35

40

45

50

Comp. No.	R <sup>1</sup>	Y
6.		CH <sub>2</sub>
7.		CH <sub>2</sub>
8.		CH <sub>2</sub>
9		CH <sub>2</sub>
10.		CH <sub>2</sub>
11.		CH <sub>2</sub>

55

5

10

15

20

25

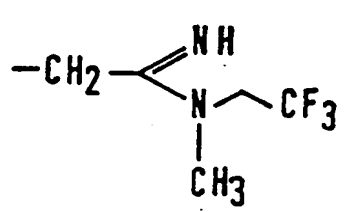
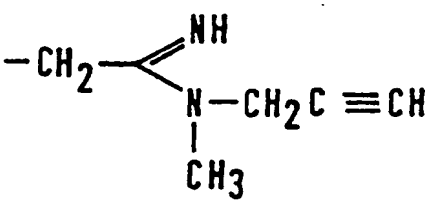
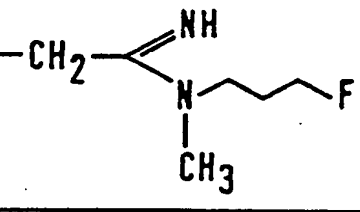
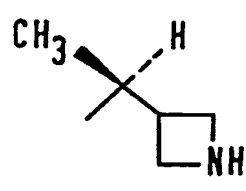
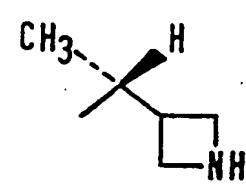
30

35

40

45

50

Comp. No.	R <sup>1</sup>	Y
12.		CH <sub>2</sub>
13.		CH <sub>2</sub>
14.		CH <sub>2</sub>
15.		CH <sub>2</sub>
16.		CH <sub>2</sub>

55

5

10

15

20

25

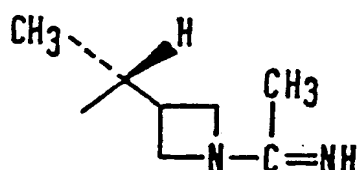
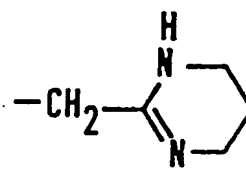
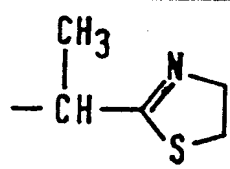
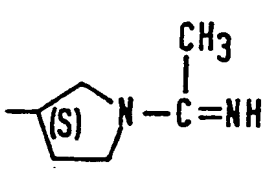
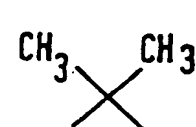
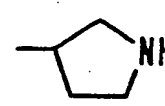
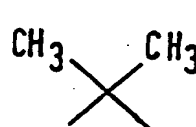
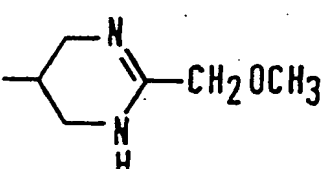
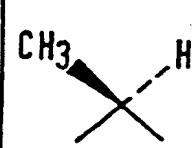
30

35

40

45

50

Comp. No.	R <sup>1</sup>	Y
17.		CH <sub>2</sub>
18.		CH <sub>2</sub>
19.		CH <sub>2</sub>
20.		
21.		
22.		

55

5

10

15

20

25

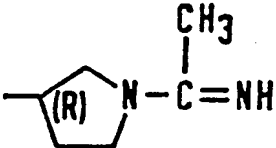

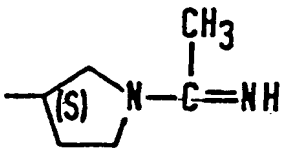


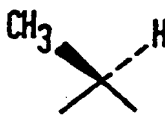
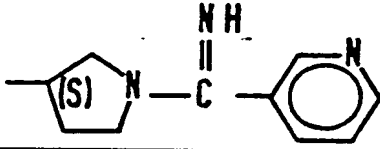
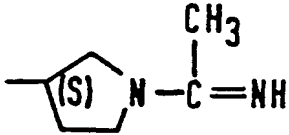
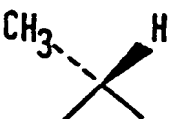
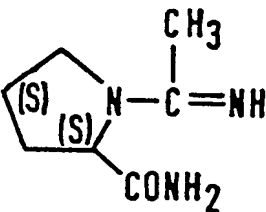
30

35

40

45

50

Comp. No.	R <sup>1</sup>	Y
23.		
24.		
25.		
26.		CH <sub>2</sub>
27.		
28.		CH <sub>2</sub>

55



5

10

15

20

25

30

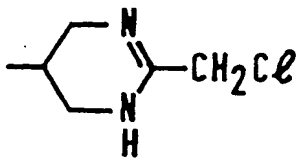
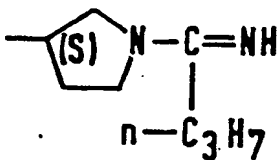
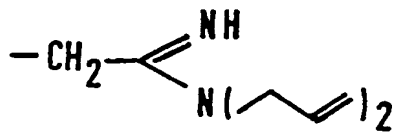
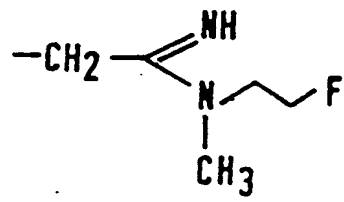

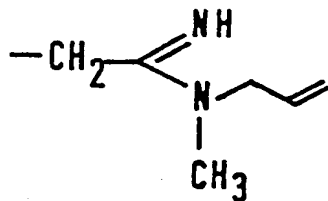
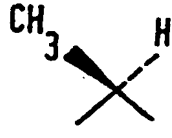
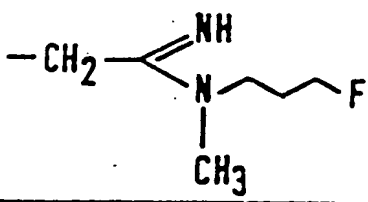
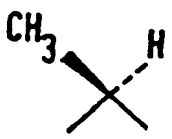
35

40

45

50

55

Comp. No.	R <sup>1</sup>	Y
29.		CH <sub>2</sub>
30.		CH <sub>2</sub>
31.		CH <sub>2</sub>
32.		
33.		
34.		

5

10

15

20

25

30

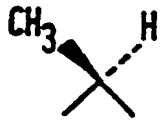

35

40

45

50

55

Comp. No.	R <sup>1</sup>	Y
35.	$-\text{CH}_2-\text{C}(\text{NH})(\text{N}(\text{CH}_2\text{CH}=\text{CH}_2)_2)$	
36.	$-\text{CH}_2\text{CH}_3$	S
37.	$-\text{CH}_2\text{CH}_2\text{F}$	S
38.		S
39.	$-\text{CH}_2\text{CN}$	S
40.	$-\text{CH}(\text{CN})\text{CH}_3$	S
41.	$-\text{CH}(\text{CONH}_2)\text{CH}_3$	S
42.	$-\text{CH}_2\text{CH}_2\text{NH}_2$	S
43.	$-\text{CH}(\text{CH}_3)\text{CH}_2\text{CN}$	$\text{CH}_2$

5

10

15

20

25

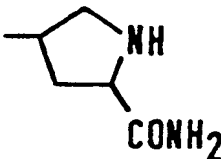
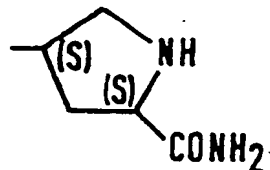
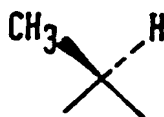

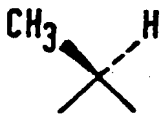
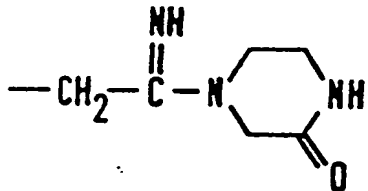
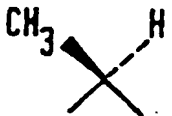
30

35

40

45

50

Comp. No.	R <sup>1</sup>	Y
44.	$\begin{array}{c} \text{—CHCH}_2\text{CN} \\   \\ \text{CH}_3 \end{array}$	S
45.	$\text{—CH}_2\text{CH}_2\text{CN}$	CH <sub>2</sub>
46.	$\begin{array}{c} \text{—CHCN} \\   \\ \text{CH}_3 \end{array}$	CH <sub>2</sub>
47.		CH <sub>2</sub>
48.		
49.		
50.		

55

5

10

15

20

25

30

35

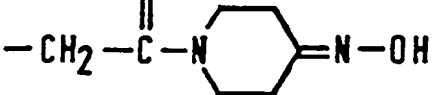
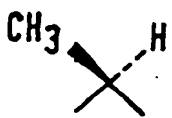
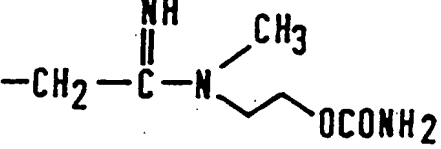
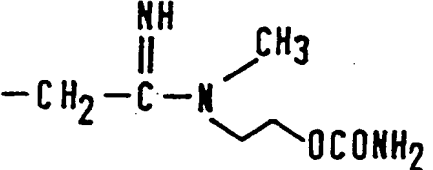

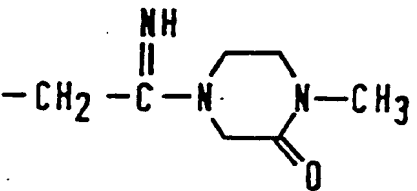
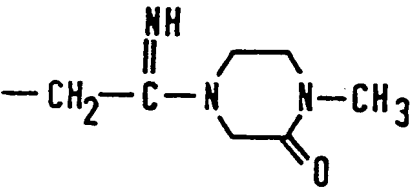

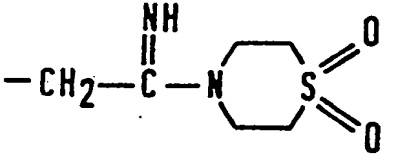
40

45

50

55

Comp. No.	R <sup>1</sup>	Y
51.		CH <sub>2</sub>
52.		CH <sub>2</sub>
53.		
54.		CH <sub>2</sub>
55.		
56.		CH <sub>2</sub>

Comp. No.	R <sup>1</sup>	Y
57.	$-\text{CH}_2-\text{C}(\text{NH})=\text{N}-\text{OH}$ 	
58.	$-\text{CH}_2-\text{C}(\text{NH})=\text{N}-\text{CH}_2\text{CH}_2\text{OCONH}_2$ 	CH <sub>2</sub>
59.	$-\text{CH}_2-\text{C}(\text{NH})=\text{N}-\text{CH}_2\text{CH}_2\text{OCONH}_2$ 	
60.	$-\text{CH}_2-\text{C}(\text{NH})=\text{N}-\text{CH}_2\text{CH}_2\text{OCONH}_2$ 	CH <sub>2</sub>
61.	$-\text{CH}_2-\text{C}(\text{NH})=\text{N}-\text{CH}_2\text{CH}_2\text{OCONH}_2$ 	
62.	$-\text{CH}_2-\text{C}(\text{NH})=\text{N}-\text{CH}_2\text{CH}_2\text{OCONH}_2$ 	CH <sub>2</sub>

5

10

15

20

25

30

35

40

45

50

55

Comp. No.	R <sup>1</sup>	Y
63.	$  \begin{array}{c}  \text{NH} \\  \parallel \\  -\text{CH}_2-\text{C}-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{S} \quad \text{S} \\ \parallel \quad \parallel \\ \text{O} \quad \text{O} \end{array}  \end{array}  $	
64.	$  \begin{array}{c}  \text{NH} \\  \parallel \\  -\text{CH}_2-\text{C}-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{S} \quad \text{S} \\ \parallel \quad \parallel \\ \text{O} \quad \text{O} \end{array}  \end{array}  $	CH <sub>2</sub>
65.	$  \begin{array}{c}  \text{NH} \\  \parallel \\  -\text{CH}_2-\text{C}-\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{S} \quad \text{S} \\ \parallel \quad \parallel \\ \text{O} \quad \text{O} \end{array}  \end{array}  $	
66.	$  \begin{array}{c}  \text{CONH}_2 \\    \\  \text{C}=\text{NH} \\    \\  \text{CH}_3  \end{array}  $	CH <sub>2</sub>
67.	$  \begin{array}{c}  \text{CONH}_2 \\    \\  \text{C}=\text{NH} \\    \\  \text{CH}_3  \end{array}  $	
68.	$  \begin{array}{c}  \text{CONH}_2 \\    \\  \text{C}=\text{NH} \\    \\  \text{CH}_3  \end{array}  $	

5

10

15

20

25

30

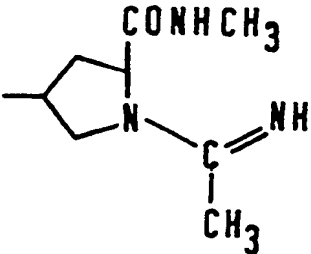
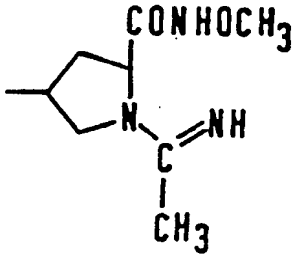
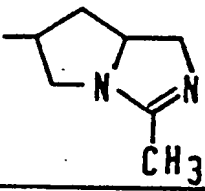
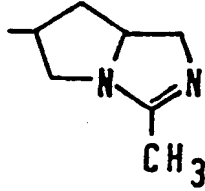
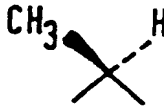
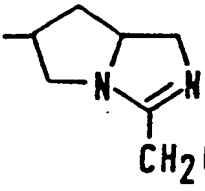
35

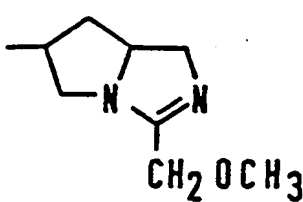

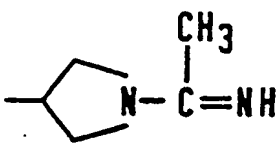
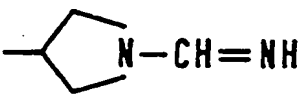
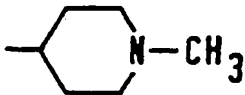
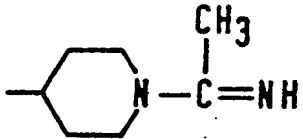
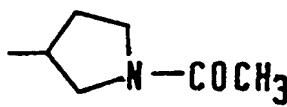
40

45

50

55

Comp. No.	R <sup>1</sup>	Y
69.		CH <sub>2</sub>
70.		CH <sub>2</sub>
71.		CH <sub>2</sub>
72.		
73.		CH <sub>2</sub>

Comp. No.	R <sup>1</sup>	Y
74.		
75.		CH <sub>2</sub>
76.		CH <sub>2</sub>
77.		CH <sub>2</sub>
78.		CH <sub>2</sub>
79.		CH <sub>2</sub>

Of the compounds listed above, we particularly prefer those which have the same configuration as thienamycin, i.e. (5R,6S)-6-[1(R)-hydroxyethyl]. In particular, the following compounds are preferred:

(5R,6S)-2-{2-[(aminomethylene)amino]ethylthio}-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid -  
(isomer of Compound No. 1)

(5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid -  
(isomer of Compound No. 6)

(5R,6S)-2-[(3R)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid -  
(isomer of Compound No. 7)

(5R,6S)-2-[(3R)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1( S)-methyl-2-carbapenem-3-carboxylic acid (isomer of Compound No. 23)

(5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1( R)-methyl-2-carbapenem-3-carboxylic acid (isomer of Compound No. 24)



(5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(S)-methyl-2-carbapenem-3-carboxylic acid (isomer of Compound No. 27)

(5R,6S)-2-[(3S)-1-acetimidoyl-5(S)-carbamoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid (isomer of Compound No. 28)

5 The above compounds may likewise be employed in the form of their pharmaceutically acceptable salts or esters, examples of which are well-known to those skilled in the art and which are given, for example, in US Patent No. 4,552,873.

The protective effect against renal toxicity appears to be exhibited by the whole range of amino acids wherein the amino and carboxylic acid groups are attached to a saturated aliphatic carbon chain or carbon atom. However, we have found that best results are achieved when employing N-acylated derivatives of those amino acids which may be represented by the formula (II):

$H_2N-X-COOH$  (II)

wherein X represents a  $C_1-C_{10}$  alkylene group or a  $C_1-C_{10}$  alkylene group having at least one substituent selected from hydroxy groups,  $C_1-C_4$  alkoxy groups,  $C_6-C_{10}$  aryloxy groups, substituted  $C_6-C_{10}$  aryloxy groups,  $C_7-C_8$  aralkyloxy groups, substituted  $C_7-C_8$  aralkyloxy groups, mercapto groups,  $C_1-C_4$  alkylthio groups,  $C_6-C_{10}$  arylthio groups, substituted  $C_6-C_{10}$  arylthio groups,  $C_7-C_8$  aralkylthio groups, substituted  $C_7-C_8$  aralkylthio groups,  $C_2-C_3$  carboxyalkylthio groups, amino groups, amino groups having one or two substituents selected from

$C_1-C_4$  alkyl groups,  $C_6-C_{10}$  aryl groups, substituted  $C_6-C_{10}$  aryl groups,  $C_7-C_8$  aralkyl groups, substituted  $C_7-C_8$  aralkyl groups and carboxylic acyl groups,

$C_6-C_{10}$  aryl groups, substituted  $C_6-C_{10}$  aryl groups, carboxy groups, amidino groups, sulpho groups,  $C_1-C_4$  alkylsulphonyl groups,  $C_1-C_4$  alkylsulphonyl groups and heterocyclic groups having from 5 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, said substituted aryloxy, aralkyloxy, arylthio, aralkylthio, aryl and aralkyl groups having at least one substituent selected from  $C_1-C_4$  alkyl groups, hydroxy groups, amino groups and  $C_1-C_4$  alkoxy groups.

In general terms, the N-acylated derivatives of these amino acids may be represented by the formula - (III):

$R^2HN-X-COOH$  (III)

wherein  $R^2$  represents a carboxylic acyl group and X is as defined above.

30 Examples of carboxylic acyl groups which may be represented by  $R^2$  include:

alkanoyl groups, and preferably alkanoyl groups having from 1 to 18, more preferably from 1 to 10 and still more preferably from 1 to 8, e.g. from 2 to 5 or from 5 to 8, carbon atoms, for example the acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, heptanoyl, octanoyl, nonanoyl and decanoyl groups; in the case of those amino acids which have relatively bulky and lipophilic groups, lower - (e.g.  $C_2-C_3$ ) alkanoyl groups are preferred; for others (e.g. glycine), higher (e.g.  $C_6-C_8$ ) groups are preferred; alkenoyl and alkynoyl groups, and more preferably such groups having from 3 to 8, more preferably 3 or 4, carbon atoms, for example the acryloyl, methacryloyl, crotonoyl or propioloyl groups;

aromatic acyl groups in which the aryl ring is a carbocyclic ring having from 6 to 14, preferably 6 to 10, carbon atoms and optionally having from 1 to 5, more preferably from 1 to 3, substituents preferably selected from  $C_1-C_4$  alkyl groups, hydroxy groups,  $C_1-C_4$  alkoxy groups, amino groups, sulpho groups and halogen atoms, for example the benzoyl and naphthoyl (1-or 2-naphthoyl) groups and the benzoyl and naphthoyl (1-or 2-naphthoyl) groups having one or more of the above substituents, for example the *p*-toluoyl, *m*-toluoyl, *o*-toluoyl, 4-butylbenzoyl, 4-hydroxybenzoyl, 3-hydroxybenzoyl, 2-hydroxybenzoyl, 4-methoxybenzoyl, 3-methoxybenzoyl, 2-methoxybenzoyl, 4-butoxybenzoyl, 4-aminobenzoyl, 3-aminobenzoyl, 4-aminobenzoyl, 3-sulphobenzoyl, 4-chlorobenzoyl, 3-fluorobenzoyl, 2-bromobenzoyl, 3-hydroxy-2-naphthoyl and 1-hydroxy-2-naphthoyl groups;

alicyclic acyl groups in which the carbocyclic ring has unsubstituted or has at least one  $C_1-C_4$  alkyl and/or phenyl substituent, for example the cyclopropanecarbonyl, cyclobutanecarbonyl, cyclopentanecarbonyl, cyclohexanecarbonyl, 1-phenyl-1-cyclopropanecarbonyl, 1-phenyl-1-cyclopentanecarbonyl, 1-methyl-1-cyclohexanecarbonyl and 1-phenyl-1-cyclohexanecarbonyl groups;

araliphatic acyl groups in which the aryl ring is a carbocyclic ring having from 6 to 14, preferably 6 to 10, carbon atoms and optionally having from 1 to 5, more preferably from 1 to 3, substituents preferably selected from  $C_1-C_4$  alkyl groups, hydroxy groups,  $C_1-C_4$  alkoxy groups, amino groups, sulpho groups and halogen atoms, and in which the alkyl moiety has from 1 to 4 carbon atoms, such as the phenylacetyl,  $\alpha$ -phenyl- $\alpha$ -methylacetyl,  $\alpha$ -phenyl- $\alpha$ -ethylacetyl,  $\alpha,\alpha$ -diphenylacetyl,  $\alpha$ -phenyl- $\alpha$ -cyclopentyl-acetyl, 3-phenylpropionyl, 4-phenylbutyryl, 4-tolylacetyl, 4-hydroxyphenylacetyl, 4-aminophenylacetyl, 4-methoxyphenylacetyl, 3-sulphophenylacetyl and 4-chlorophenylacetyl groups;

heterocyclic acyl groups which may have saturated or unsaturated ring systems, the rings having 5 or 6

ring atoms, of which from 1 to 3 are nitrogen and/or sulphur and/or oxygen hetero-atoms and the ring being unsubstituted or having from 1 to 3 C,-C<sub>4</sub> alkyl and/or hydroxy substituents, for example the nicotinoyl, 2-thiophenecarbonyl, 2-furoyl, 2-pyrazinecarbonyl, 2-piperidinecarbonyl, N-methylnicotinoyl and 6-hydroxynicotinoyl groups;

- 5 alkoxy carbonyl groups having a total of from 2 to 7 carbon atoms, for example the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl and pentyloxycarbonyl groups; and

- 10 aralkyloxycarbonyl groups in which the aralkyl moiety has from 7 to 9 carbon atoms and is unsubstituted or has from 1 to 5, more preferably from 1 to 3, substituents selected from amino groups, C,-C<sub>4</sub> alkyl groups, C,-C<sub>4</sub> alkoxy groups and hydroxy groups, for example the benzyloxycarbonyl,  $\alpha$ -methylbenzyloxycarbonyl, phenethyloxycarbonyl, 3-phenylpropoxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-hydroxybenzyloxycarbonyl, *p*-tolylloxycarbonyl and 4-aminobenzyloxycarbonyl groups.

- In addition to the acyl groups listed above, R<sup>2</sup> can also represent an acyl group derived from an amino acid by removal of OH from the carboxylic acid group and N-acylation of the amino group with at least one  
15 of the above-mentioned acyl groups. Hence, R<sup>2</sup> can also represent such an acyl group connected to the parent amino acid via one or more amino acid residues, preferably from 0 to 5, more preferably from 0 to 3 and most preferably from 0 to 2, such residues. Thus, R<sup>2</sup> could represent a group derived from an N-acylated amino acid, for example the N-benzoylglycyl or N-benzoylglycylglycyl group. Hence, compounds of formula (I) also include such oligopeptide compounds as N-benzoylglycylglycine, N-benzoylglycylglycylglycine and similar compounds.

- Preferred examples of groups which may be represented by R<sup>2</sup> include: saturated aliphatic acyl groups having from 1 to 8 carbon atoms; aromatic acyl groups in which the aryl moiety has from 6 to 10 ring carbon atoms and is unsubstituted or has from 1 to 3 C,-C<sub>4</sub> alkyl and/or C,-C<sub>4</sub> alkoxy substituents; alicyclic acyl groups in which the cycloalkane ring has from 3 to 6 carbon atoms; araliphatic acyl groups in which  
25 the aryl ring has from 6 to 10 ring carbon atoms and the alkyl group has from 1 to 4 carbon atoms, the aryl ring being unsubstituted or having from 1 to 3 C,-C<sub>4</sub> alkyl and/or C,-C<sub>4</sub> alkoxy substituents; heterocyclic acyl groups in which the heterocyclic ring is saturated or unsaturated and has 5 or 6 ring atoms of which one is a nitrogen, sulphur or oxygen hetero-atom; alkoxy carbonyl groups having a total of from 2 to 7 carbon atoms; and aralkyloxycarbonyl groups in which the aralkyl moiety has from 7 to 9 carbon atoms and the  
30 aryl ring is unsubstituted or has from 1 to 3 C,-C<sub>4</sub> alkyl and/or C,-C<sub>4</sub> alkoxy substituents.

- Particularly preferred groups which may be represented by R<sup>2</sup> include: aromatic acyl groups in which the aryl ring has from 6 to 10 ring atoms and which is unsubstituted or has a single substituent selected from C,-C<sub>4</sub> alkyl groups, C,-C<sub>4</sub> alkoxy groups, hydroxy groups and amino groups; alicyclic acyl groups in which the cycloalkane moiety has from 3 to 6 carbon atoms; phenylaliphatic acyl groups in which the  
35 phenyl group is unsubstituted or has a single C,-C<sub>4</sub> alkyl substituent, and in which the alkyl part has from 1 to 4 carbon atoms; alkoxy carbonyl groups having a total of from 4 to 6 carbon atoms; and aralkyloxycarbonyl groups in which the aralkyl part has from 7 to 9 carbon atoms and has 0 or 1 C,-C<sub>4</sub> alkyl or C,-C<sub>4</sub> alkoxy substituent.

- In addition, such acyl groups linked to the amino acid via at least one further amino acid residue are  
40 preferred.

- Of the groups exemplified above, the following are most preferred: acetyl, benzoyl, cyclohexanecarbonyl, cyclopropanecarbonyl, hexanoyl, isobutyryl, crotonoyl, ethoxycarbonyl, 4-hydroxybenzoyl, anisoyl, 4-aminobenzoyl, naphthoyl, toluoyl, benzyloxycarbonyl and 4-methoxybenzyloxycarbonyl groups, of which the acetyl and benzoyl, particularly benzoyl, groups are most preferred. As explained previously, the lower  
45 alkanoyl groups, notably the acetyl group, are only most preferred in relation to their use with those amino acids which have relatively bulky and lipophilic groups.

- In the compounds of formula (II), X represents an alkylene group having from 1 to 10, preferably from 1 to 8 and more preferably from 1 to 5, carbon atoms. Such groups may have the "free" valencies attached to different carbon atoms or to the same carbon atom. In the latter case, the groups are sometimes referred  
50 to as "alkylidene" groups. Examples include the methylene, ethylidene, ethylene, propylidene, 1-methylethylidene, 1-methylethylene, trimethylene, butylidene, 2-methylpropylidene, 1-methylpropylidene, 1,2-dimethylethylene, 1-ethylethylene, 1-methyltrimethylene, 2-methyltrimethylene, tetramethylene, pentylidene, 3-methylbutylidene, 2-methylbutylidene, 2,2-dimethylpropylidene, 1-ethylpropylidene, 1,2-dimethylpropylidene, 1-propylethylene, 1-(1-methylethyl)ethylene, 1-ethyl-2-methylethylene, 1-ethyltrimethylene, 2-ethyltrimethylene, 1,3-dimethyltrimethylene, 1-methyltetramethylene, 2-methyltetramethylene, pentamethylene, hexylidene, 4-methylpentylidene, 3-methylpentylidene, 2-methylpentylidene, 1-methylpentylidene, 2-ethylbutylidene, 1-ethylbutylidene, 1,3-dimethylbutylidene, 1,2-dimethylbutylidene, 3,3-dimethylbutylidene, 2,3-dimethylbutylidene, 1-butylethylene, 1-methyl-2-propylethylene, 1,2-diethylethylene, 1-

methyl-1-propylethylene, 2-propyltrimethylene, 1-ethyl-3-methyltrimethylene, 1-ethyltetramethylene, 2-ethyltetramethylene, 1,3-dimethyltetramethylene, 1-methylpentamethylene, 2-methylpentamethylene, 3-methylpentamethylene, hexamethylene, heptylidene, 5-methylhexylidene, 4-methylhexylidene, 3-methylhexylidene, 1-methylhexylidene, 3-ethylpentylidene, 1-ethylpentylidene, 4,4-dimethylpentylidene, 2,4-dimethylpentylidene, 1,2-dimethylpentylidene, 1-propylbutylidene, 2-ethyl-1-methylbutylidene, 1-ethyl-2-methylbutylidene, 1,2,2-trimethylbutylidene, 1,2,3-trimethylbutylidene, 1-pentylethylene, 1-butyl-2-methylethylene, 1-ethyl-2-propylethylene, 1-butyl-1-methylethylene, 1-ethyl-1-propylethylene, 1-butyltrimethylene, 2-butyltrimethylene, 1,3-diethyltrimethylene, 1-methyl-3-propyltrimethylene, 1-propyltetramethylene, 2-propyltetramethylene, 1-ethyl-4-methyltetramethylene, 3-ethyl-1-methyltetramethylene, 1-ethylpentamethylene, 3-ethylpentamethylene, 1,3-dimethylpentamethylene, 1-methylhexamethylene, 3-methylhexamethylene, heptamethylene, octylidene, 6-methylheptylidene, 4-methylheptylidene, 2-methylheptylidene, 1-methylheptylidene, 4-ethylhexylidene, 3-ethylhexylidene, 2-ethylhexylidene, 1-ethylhexylidene, 3,5-dimethylhexylidene, 4,5-dimethylhexylidene, 2,4-dimethylhexylidene, 1,5-dimethylhexylidene, 1,4-dimethylhexylidene, 2-propylpentylidene, 1-propylpentylidene, 2-ethyl-4-methylpentylidene, 3-ethyl-2-methylpentylidene, 3-ethyl-1-methylpentylidene, 1-ethyl-3-methylpentylidene, 3-methyl-1-propylbutylidene, 2-methyl-1-propylbutylidene, 1-ethyl-2,3-dimethylbutylidene, 1,2-diethylbutylidene, 1-hexylethylene, 1-methyl-2-pentylethylene, 1-butyl-2-ethylethylene, 1,2-dipropylethylene, 1-pentyltrimethylene, 2-pentyltrimethylene, 1-butyl-3-methyltrimethylene, 1-butyl-2-methyltrimethylene, 1-ethyl-3-propyltrimethylene, 1,2-dimethyl-3-propyltrimethylene, 1-butyltetramethylene, 1-methyl-4-propyltetramethylene, 1-propylpentamethylene, 3-propylpentamethylene, 2-ethyl-4-methylpentamethylene, 1-ethylhexamethylene, 3-ethylhexamethylene, 1,3-dimethylhexamethylene, 1-methylheptamethylene, 4-methylheptamethylene and octamethylene groups.

The alkylene group represented by X, including those alkylene groups exemplified above, may be unsubstituted or may have at least 1, preferably from 1 to 4 and more preferably 1 or 2, substituents selected from the following groups:

hydroxy groups;

C<sub>1</sub>-C<sub>4</sub> alkoxy groups, for example the methoxy or ethoxy groups;

aryloxy groups in which the aryl ring has from 6 to 14, more preferably from 6 to 10, ring carbon atoms and which is unsubstituted or has from 1 to 5, more preferably from 1 to 3, substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups, for example the phenoxy, *p*-tolylloxy, 4-hydroxyphenoxy, 4-aminophenoxy and 4-methoxyphenoxy groups;

C<sub>1</sub>-C<sub>4</sub> aralkyloxy groups in which the aryl ring is unsubstituted or has from 1 to 5, more preferably from 1 to 3, substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups, for example the benzyloxy, 4-methylbenzyloxy, 4-hydroxybenzyloxy, 4-aminobenzyloxy and 4-methoxybenzyloxy groups;

mercapto groups;

C<sub>1</sub>-C<sub>4</sub> alkylthio groups, for example the methylthio or ethylthio groups;

arylthio groups in which the aryl ring has from 6 to 14, more preferably from 6 to 10, ring carbon atoms and which is unsubstituted or has from 1 to 5, more preferably from 1 to 3, substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups, for example the phenylthio, *p*-tolylthio, 4-hydroxyphenylthio, 4-aminophenylthio and 4-methoxyphenylthio groups;

C<sub>1</sub>-C<sub>4</sub> aralkylthio groups in which the aryl ring is unsubstituted or has from 1 to 5, more preferably from 1 to 3, substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups, for example the benzylthio, 4-methylbenzylthio, 4-hydroxybenzylthio, 4-aminobenzylthio and 4-methoxybenzylthio groups;

carboxyalkylthio groups having from 1 to 4 carbon atoms in the alkyl moiety, for example the carboxymethylthio and carboxyethylthio groups;

amino groups;

amino groups having one or two C<sub>1</sub>-C<sub>4</sub> alkyl substituents, for example the methylamino, ethylamino and dimethylamino groups;

amino groups having one or two aryl substituents, wherein the aryl ring has from 6 to 14 ring carbon atoms and is unsubstituted or has from 1 to 5, preferably from 1 to 3, substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups, and C<sub>1</sub>-C<sub>4</sub> alkoxy groups, such as the phenylamino, *p*-tolylamino, 4-hydroxyphenylamino, 4-aminophenylamino and 4-methoxyphenylamino groups;

amino groups having one or two C<sub>1</sub>-C<sub>4</sub> aralkyl substituents wherein the aryl moiety is unsubstituted or has from 1 to 5, preferably from 1 to 3, substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkyl groups, such as the benzylamino, 4-methylbenzylamino, 4-hydroxybenzylamino, 4-aminobenzylamino and 4-methoxybenzylamino groups;

amino groups substituted by one or two carboxylic acyl groups as defined in relation to R<sup>2</sup>;

aryl groups having from 6 to 14 ring carbon atoms, and being unsubstituted or having from 1 to 5, preferably from 1 to 3, substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups;

carboxy groups;

5 amidino groups;

sulpho groups;

C<sub>1</sub>-C<sub>4</sub> alkylsulphinyl groups, such as the methanesulphinyl or ethanesulphinyl groups;

C<sub>1</sub>-C<sub>4</sub> alkylsulphonyl groups, such as the methanesulphonyl or ethanesulphonyl groups; and

10 heterocyclic groups, such as the pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolaziny, indolyl and indazolyl groups.

Preferred groups which may be represented by X include C<sub>1</sub>-C<sub>4</sub> alkylene groups which are unsubstituted or have one or two substituents selected from: hydroxy groups; C<sub>1</sub>-C<sub>4</sub> alkoxy groups; aryloxy groups wherein the aryl ring has from 6 to 14 ring carbon atoms and which is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; C<sub>1</sub>-C<sub>4</sub> aralkyloxy groups, wherein the aryl moiety is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; mercapto groups; C<sub>1</sub>-C<sub>4</sub> alkylthio groups; arylthio groups wherein the aryl ring has from 6 to 14 ring carbon atoms and which is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; C<sub>1</sub>-C<sub>4</sub> aralkylthio groups wherein the aryl ring is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups;

20 carboxyalkylthio groups in which the alkyl part has from 1 to 4 carbon atoms; amino groups; amino groups having one or two C<sub>1</sub>-C<sub>4</sub> alkyl substituents; amino groups having one or two aryl substituents in which the aryl ring has from 6 to 14 ring carbon atoms and is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; amino groups having one or two C<sub>1</sub>-C<sub>4</sub> aralkyl substituents in which the aryl part is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; amino groups having one or two carboxylic acyl substituents as defined in relation to R<sup>2</sup>; aryl groups having from 6 to 14 ring carbon atoms and being unsubstituted or having from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; carboxy groups; and heterocyclic groups having from 5 to 9 ring atoms, of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur hetero-atoms.

More preferred groups which may be represented by X are C<sub>1</sub>-C<sub>4</sub> alkylene groups which are unsubstituted or have 1 or 2 substituents selected from: hydroxy groups; C<sub>1</sub>-C<sub>4</sub> alkoxy groups; mercapto groups; C<sub>1</sub>-C<sub>4</sub> alkylthio groups; amino groups; amino groups having one or two C<sub>1</sub>-C<sub>4</sub> alkyl substituents; amino groups having one or two carboxylic acyl substituents as defined for R<sup>2</sup>; aryl groups having from 6 to 14 carbon atoms wherein the aryl ring is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; carboxy groups; and heterocyclic groups having from 5 to 9 ring atoms, of which from 1 to 3 are nitrogen and/or oxygen hetero-atoms.

Preferred amino acids which may be represented by formula (II) include glycine, β-alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, 8-aminooctanoic acid, alanine, 2-aminobutyric acid, norvaline, valine, leucine, isoleucine, norleucine, tyrosine, O-methyltyrosine, aspartic acid, glutamic acid, 4-carboxyglutamic acid, 3-methylaspartic acid, 2-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid, 3-hydroxyaspartic acid, 3-hydroxyglutamic acid, 2,3-diaminopropionic acid, 2,4-diaminobutyric acid, 5-hydroxylysine, arginine, N<sup>δ</sup>,N<sup>δ</sup>-dimethylornithine, N<sup>ε</sup>-methyllysine, cysteine, methionine, 45 ethionine, S-carboxymethylcysteine, S-benzylcysteine, methionine S-oxide, ethionine S-oxide, methionine S,S-dioxide, cysteic acid, serine, O-methylserine, threonine, O-methylthreonine, homothreonine, ethoxinine (= 2-amino-4-ethoxybutyric acid), 3-methoxyvaline, 3-phenylserine, 3-methyl-3-phenylalanine, histidine, tryptophan, 2-methylalanine, 2-methylserine, 2-hydroxyisoleucine, 2-methylmethionine, 2-ethyl-2-phenylglycine, 3-aminobutyric acid, 3-amino-4-methylvaleric acid, 3-amino-3-phenylpropionic acid, 3-amino-2-hydroxypropionic acid and 4-amino-3-hydroxybutyric acid.

More preferred amino acids are glycine, β-alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, 8-aminooctanoic acid, alanine, norvaline, valine, leucine, isoleucine, norleucine, N<sup>δ</sup>,N<sup>δ</sup>-dimethylornithine, methionine, ethionine, O-methylserine, O-methylthreonine, ethoxinine, 3-methoxyvaline, 3-phenylserine, 3-methyl-3-phenylalanine, histidine, 2-methylalanine, 2-methylserine, 2-hydroxyisoleucine, 2-ethylphenylglycine, 3-aminobutyric acid, 3-amino-4-methylvaleric acid and 3-amino-3-phenylpropionic acid.

The most preferred amino acids are β-alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, alanine, valine, leucine, norleucine, methionine, histidine and glycine.

When the amino acid derivative is an oligopeptide compound, such as a dipeptide or tripeptide, this type of compound is preferably formed by suitable combination of such amino acids as glycine,  $\beta$ -alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, alanine, valine, leucine, norleucine, phenylglycine, phenylalanine, methionine and histidine. Examples include leucylglycine, glycyL- $\beta$ -alanine, glycyLalanine, valylalanine, leucylalanine, glycyLvaline, alanylvaline, leucylvaline, valylleucine, phenylalanylleucine, histidylleucine, glycyLphenylalanine, alanylphenylalanine, leucylphenylalanine, glycyLmethionine, valylmethionine, glycyLhistidine, alanylvalylglycine, glycyLalanylvaline, glycyLphenylalanylleucine and glycyLglycyLhistidine.

Specific examples of the amino acid compounds which may be employed in the present invention are given in the following list. It should, of course, be appreciated that these compounds can exist in the D-, L- and DL-forms and any of these forms can be employed. The compounds are hereinafter referred to by the numbers appended to them in this list. In the case of the amino acids having 2 or more amino groups (e.g. 2,3-diaminopropionic acid, 2,4-diaminobutyric acid and arginine), mono-acylated derivatives (in which the acyl group can be on any amino group) and polyacylated derivatives are possible.

### 1. Glycine derivatives.

- 1-1. N-hexanoylglycine
- 1-2. N-heptanoylglycine
- 1-3. N-octanoylglycine
- 1-4. N-nonanoylglycine
- 1-5. N-decanoylglycine
- 1-6. N-(p-toluoyl)glycine
- 1-7. N-(4-methoxybenzoyl)glycine
- 1-8. N-(1-naphthoyl)glycine
- 1-9. N-(1-phenyl-1-cyclohexanecarbonyl)glycine
- 1-10. N-( $\alpha,\alpha$ -diphenylacetyl)glycine
- 1-11. N-( $\alpha$ -phenyl- $\alpha$ -cyclopentylacetyl)glycine
- 1-12. N-butoxycarbonylglycine
- 1-13. N-octanoylleucylglycine
- 1-14. N-benzoylleucylglycine
- 1-15. N-butoxycarbonylleucylglycine
- 1-16. N-octanoylalanylvalylglycine
- 1-17. N-benzoylalanylvalylglycine
- 1-18. N-cyclohexanecarbonylalanylvalylglycine
- 1-19. N-butoxycarbonylalanylvalylglycine

### 3. $\beta$ -Alanine derivatives.

- 2-1. N-hexanoyl- $\beta$ -alanine
- 2-2. N-heptanoyl- $\beta$ -alanine
- 2-3. N-octanoyl- $\beta$ -alanine
- 2-4. N-nonanoyl- $\beta$ -alanine
- 2-5. N-(p-toluoyl)- $\beta$ -alanine
- 2-6. N-(4-methoxybenzoyl)- $\beta$ -alanine
- 2-7. N-(3-hydroxy-2-naphthoyl)- $\beta$ -alanine
- 2-8. N-(1-phenyl-1-cyclopentanecarbonyl)- $\beta$ -alanine
- 2-9. N-( $\alpha,\alpha$ -diphenylacetyl)- $\beta$ -alanine
- 2-10. N-(3-phenylpropionyl)- $\beta$ -alanine
- 2-11. N-(4-phenylbutyryl)- $\beta$ -alanine
- 2-12. N-(4-methoxyphenylacetyl)- $\beta$ -alanine
- 2-13. N-t-butoxycarbonyl- $\beta$ -alanine
- 2-14. N-benzyloxycarbonyl- $\beta$ -alanine
- 2-15. N-(4-methoxybenzyloxycarbonyl)- $\beta$ -alanine
- 2-16. N-(4-methylbenzyloxycarbonyl)- $\beta$ -alanine
- 2-17. N-( $\alpha$ -methylbenzyloxycarbonyl)- $\beta$ -alanine

- 2-18. N -benzoylglycyl- $\beta$ -alanine  
 2-19. N-(1-naphthoyl)glycyl- $\beta$ -alanine  
 2-20. N-cyclohexanecarbonylglycyl- $\beta$ -alanine  
 2-21. N-benzyloxycarbonylglycyl- $\beta$ -alanine  
 2-22. N-benzoyl- $\beta$ -alanine

5

#### 4-Aminobutyric acid derivatives.

- 10 3-1. N-hexanoyl-4-aminobutyric acid  
 3-2. N-heptanoyl-4-aminobutyric acid  
 3-3. N-benzoyl-4-aminobutyric acid  
 3-4. N-(p-toluoyl)-4-aminobutyric acid  
 3-5. N-(3-methoxybenzoyl)-4-aminobutyric acid  
 15 3-6. N-cyclopentanecarbonyl-4-aminobutyric acid  
 3-7. N-cyclohexanecarbonyl-4-aminobutyric acid  
 3-8. N-(1-phenyl-1-cyclopropanecarbonyl)-4-aminobutyric acid  
 3-9. N-(1-phenyl-1-cyclopentanecarbonyl)-4-aminobutyric acid  
 3-10. N-phenylacetyl-4-aminobutyric acid  
 20 3-11. N-(3-phenylpropionyl)-4-aminobutyric acid  
 3-12. N-(p-tolylacetyl)-4-aminobutyric acid  
 3-13. N-nicotinoyl-4-aminobutyric acid  
 3-14. N-butoxycarbonyl-4-aminobutyric acid  
 3-15. N-benzyloxycarbonyl-4-aminobutyric acid  
 25 3-16. N-(3-phenylpropoxycarbonyl)-4-aminobutyric acid  
 3-17. N-( $\alpha$ -methylbenzyloxycarbonyl)-4-aminobutyric acid  
 3-18. N-(1-naphthoyl)-4-aminobutyric acid

#### 30 4. 5-Aminovaleric acid derivatives

- 4-1. Nbutyryl-5-aminovaleric acid  
 4-2. N-isobutyryl-5-aminovaleric acid  
 4-3. Nvaleryl-5-aminovaleric acid  
 35 4-4. N-isovaleryl-5-aminovaleric acid  
 4-5. N -hexanoyl-5-aminovaleric acid  
 4-6. N-benzoyl-5-aminovaleric acid  
 4-7. N-(m-toluoyl)-5-aminovaleric acid  
 4-8. N-(2-methoxybenzoyl)-5-aminovaleric acid  
 40 4-9. N-cyclopentanecarbonyl-5-aminovaleric acid  
 4-10. N-cyclohexanecarbonyl-5-aminovaleric acid  
 4-11. N-(1-phenyl-1-cyclopropanecarbonyl)-5-aminovaleric acid  
 4-12. N-(1-phenyl-1-cyclohexanecarbonyl)-5-aminovaleric acid.  
 4-13. N-phenylacetyl-5-aminovaleric acid  
 45 4-14. N-( $\alpha$ -phenyl- $\alpha$ -methylacetyl)-5-aminovaleric acid  
 4-15. N-nicotinoyl-5-aminovaleric acid  
 4-16. N-(2-thiophenecarbonyl)-5-aminovaleric acid  
 4-17. N-(2-furoyl)-5-aminovaleric acid  
 4-18. N-isopropoxycarbonyl-5-aminovaleric acid  
 50 4-19. N-pentyloxycarbonyl-5-aminovaleric acid  
 4-20. N-benzyloxycarbonyl-5-aminovaleric acid  
 4-21. N-(4-methoxybenzyloxycarbonyl)-5-aminovaleric acid  
 4-22. N-4-methylbenzyloxycarbonyl-5-aminovaleric acid  
 4-23. N-4-hydroxyphenylacetyl-5-aminovaleric acid  
 55 4-24. N(N-methylnicotinoyl)-5-aminovaleric acid

### 5. 6-Aminohexanoic acid derivatives.

- 5-1. N -acetyl-6-aminohexanoic acid  
 5-2. N-propionyl-6-aminohexanoic acid  
 5-3. N-butyryl-6-aminohexanoic acid  
 5-4. N-isobutyryl-6-aminohexanoic acid  
 5-5. N-isovaleryl-6-aminohexanoic acid  
 5-6. N-hexanoyl-6-aminohexanoic acid  
 5-7. N-acryloyl-6-aminohexanoic acid  
 5-8. N-methacryloyl-6-aminohexanoic acid  
 5-9. N-crotonoyl-6-aminohexanoic acid  
 5-10. N-propioloyl-6-aminohexanoic acid  
 5-11. N-benzoyl-6-aminohexanoic acid  
 5-12. N-(o -toluoyl)-6-aminohexanoic acid  
 5-13. N-(4-methoxybenzoyl)-6-aminohexanoic acid  
 5-14. N-(4-aminobenzoyl)-6-aminohexanoic acid  
 5-15. N-(1-naphthoyl)-6-aminohexanoic acid  
 5-16. N-cyclobutanecarbonyl-6-aminohexanoic acid  
 5-17. N-cyclopentanecarbonyl-6-aminohexanoic acid  
 5-18. N-cyclohexanecarbonyl-6-aminohexanoic acid  
 5-19. N-phenylacetyl-6-aminohexanoic acid  
 5-20. N-(3-phenylpropionyl)-6-aminohexanoic acid  
 5-21. N-nicotinoyl-6-aminohexanoic acid  
 5-22. N-(2-thiophenecarbonyl)-6-aminohexanoic acid  
 5-23. N-methoxycarbonyl-6-aminohexanoic acid  
 5-24. N-ethoxycarbonyl-6-aminohexanoic acid  
 5-25. N -butoxycarbonyl-6-aminohexanoic acid  
 5-26. N -pentyloxycarbonyl-6-aminohexanoic acid  
 5-27. N -benzyloxycarbonyl-6-aminohexanoic acid  
 5-28. N -phenethyloxycarbonyl-6-aminohexanoic acid  
 5-29. N-(3-phenylpropoxycarbonyl)-6-aminohexanoic acid  
 5-30. N-(4-methoxybenzyloxycarbonyl)-6-aminohexanoic acid  
 5-31. N-(4-methylbenzyloxycarbonyl)-6-aminohexanoic acid  
 5-32. N-( $\alpha$ -methylbenzyloxycarbonyl)-6-aminohexanoic acid  
 5-33. N-(N-methylnicotinoyl)-6-aminohexanoic acid  
 5-34. N-(4-chlorophenylacetyl)-6-aminohexanoic acid

### 6. 8-Aminooctanoic acid derivatives.

- 6-1. N-acetyl-8-aminooctanoic acid  
 6-2. N-valeryl-8-aminooctanoic acid  
 6-3. N-benzoyl-8-aminooctanoic acid  
 6-4. N -(3-hydroxybenzoyl)-8-aminooctanoic acid  
 6-5. N -(3-sulphobenzoyl)-8-aminooctanoic acid  
 6-6. N -cyclopropanecarbonyl-8-aminooctanoic acid  
 6-7. N -(4-aminophenylacetyl)-8-aminooctanoic acid  
 6-8. N-methoxycarbonyl-8-aminooctanoic acid  
 6-9. N -propoxycarbonyl-8-aminooctanoic acid  
 6-10. N -isopropoxycarbonyl-8-aminooctanoic acid  
 6-11. N -benzyloxycarbonyl-8-aminooctanoic acid  
 6-12. N -(4-hydroxybenzyloxycarbonyl)-8-aminooctanoic acid  
 6-13. N-(N-methylnicotinoyl)-8-aminooctanoic acid  
 6-14. N-(6-hydroxynicotinoyl)-8-aminooctanoic acid

7. Alanine derivatives.

- 7-1. N-valerylalanine  
 7-2. N-hexanoylalanine  
 5 7-3. N-benzoylalanine  
 7-4. N-(4-methoxybenzoyl)alanine  
 7-5. N-(1-naphthoyl)alanine  
 7-6. N-(1-phenyl-1-cyclopropanecarbonyl)alanine  
 7-7. N-phenylacetylalanine  
 10 7-8. N-butoxycarbonylalanine  
 7-9. N-benzyloxycarbonylalanine  
 7-10. N-( $\alpha$ -methylbenzyloxycarbonyl)alanine  
 7-11. N-octanoylglycylalanine  
 7-12. N-benzoylglycylalanine  
 15 7-13. N-butoxycarbonylglycylalanine  
 7-14. N-benzoylvalylalanine  
 7-15. N-(*p*-toluoyl)valylalanine  
 7-16. N-cyclopentanecarbonylvalylalanine  
 7-17. N-cyclohexanecarbonylvalylalanine  
 20 7-18. N-benzyloxycarbonylvalylalanine  
 7-19. N-benzoylleucylalanine  
 7-20. N-(4-methoxybenzoyl)leucylalanine  
 7-21. N-butoxycarbonylleucylalanine  
 7-22. N-benzyloxycarbonylleucylalanine  
 25 7-23. N-(2-bromobenzoyl)alanine

8. 2-Aminobutyric acid derivatives.

- 30 8-1. N-pivaloyl-2-aminobutyric acid  
 8-2. N-hexanoyl-2-aminobutyric acid  
 8-3. N-heptanoyl-2-aminobutyric acid  
 8-4. N-benzoyl-2-aminobutyric acid  
 8-5. N-(*p*-toluoyl)-2-aminobutyric acid  
 35 8-6. N-(1-phenyl-1-cyclopentanecarbonyl)-2-aminobutyric acid  
 8-7. N-( $\alpha,\alpha$ -diphenylacetyl)-2-aminobutyric acid  
 8-8. N-ethoxycarbonyl-2-aminobutyric acid  
 8-9. N-benzyloxycarbonyl-2-aminobutyric acid  
 8-10. N-(4-methoxybenzyloxycarbonyl)-2-aminobutyric acid  
 40

9. Norvaline derivatives.

- 9-1. N-valerylnorvaline  
 45 9-2. N-decanoylnorvaline  
 9-3. N-benzoylnorvaline  
 9-4. N-(*m*-toluoyl)norvaline  
 9-5. N-(3-sulphobenzoyl)norvaline  
 9-6. N-cyclohexanecarbonylnorvaline  
 50 9-7. N-(1-phenyl-1-cyclohexanecarbonyl)norvaline  
 9-8. N-( $\alpha$ -phenyl- $\alpha$ -ethylacetyl)norvaline  
 9-9. N-(4-methoxyphenylacetyl)norvaline  
 9-10. N-(2-pyrazinecarbonyl)norvaline  
 9-11. N-benzyloxycarbonylnorvaline  
 55 9-12. N-(4-methylbenzyloxycarbonyl)norvaline



Valine derivatives.

- 10-1. N-propionylvaline  
 10-2. N-butyrylvaline  
 5 10-3. N-isobutyrylvaline  
 10-4. N-valerylvaline  
 10-5. N-acryloylvaline  
 10-6. N-methacryloylvaline  
 10-7. N-crotonoylvaline  
 10 10-8. N-propioloylvaline  
 10-9. N-(2-methoxybenzoyl)valine  
 10-10. N-(4-butoxybenzoyl)valine  
 10-11. N-cyclopentanecarbonylvaline  
 10-12. N-cyclohexanecarbonylvaline  
 15 10-13. N-(1-phenyl-1-cyclopentanecarbonyl)valine  
 10-14. N-phenylacetylvaline  
 10-15. N-nicotinoylvaline  
 10-16. N-(2-piperidinecarbonyl)valine  
 10-17. N-ethoxycarbonylvaline  
 20 10-18. N-isopropoxycarbonylvaline  
 10-19. N-t-butoxycarbonylvaline  
 10-20. N-pentyloxycarbonylvaline  
 10-21. N-benzyloxycarbonylvaline  
 10-22. N-(p-tolylacetyl)valine  
 25 10-23. N-benzoylglycylvaline  
 10-24. N-(p-toluoyl)glycylvaline  
 10-25. N-(1-naphthoyl)glycylvaline  
 10-26. N-cyclopentanecarbonylglycylvaline  
 10-27. N-butoxycarbonylglycylvaline  
 30 10-28. N-octanoylalanylvaline  
 10-29. N-benzoylalanylvaline  
 10-30. N-(p-toluoyl)alanylvaline  
 10-31. N-(4-aminobenzoyl)alanylvaline  
 10-32. N-(1-naphthoyl)alanylvaline  
 35 10-33. N-cyclohexanecarbonylalanylvaline  
 10-34. N-phenylacetylalanylvaline  
 10-35. N-benzyloxycarbonylalanylvaline  
 10-36. N-benzoylleucylvaline  
 10-37. N-benzoylglycylalanylvaline  
 40 10-38. N-(p-toluoyl)glycylalanylvaline  
 10-39. N-(1-naphthoyl)glycylalanylvaline  
 10-40. N-cyclopentanecarbonylglycylalanylvaline  
 10-41. N-butoxycarbonylglycylalanylvaline  
 10-42. N-benzyloxycarbonylglycylalanylvaline  
 45 10-43. N-(N-methylnicotinoyl)valine  
 10-44. N-(3-fluorobenzoyl)valine  
 10-45. N-benzoylvaline

50 11. Leucine derivatives.

- 11-1. N-butyrylleucine  
 11-2. N-isovalerylleucine  
 11-3. N-benzoylleucine  
 55 11-4. N-(4-butylbenzoyl)leucine  
 11-5. N-(2-hydroxybenzoyl)leucine  
 11-6. N-(3-sulphobenzoyl)leucine  
 11-7. N-cyclopentanecarbonylleucine

- 11-8. N-cyclohexanecarbonylleucine  
 11-9. N-(1-phenyl-1-cyclopropanecarbonyl)leucine  
 11-10. N-phenylacetylleucine  
 11-11. N-nicotinoylleucine  
 5 11-12. N-ethoxycarbonylleucine  
 11-13. N-benzyloxycarbonylleucine  
 11-14. N-(4-hydroxyphenylacetyl)leucine  
 11-15. N-benzoylvalylleucine  
 11-16. N-ethoxycarbonylvalylleucine  
 10 11-17. N-benzoylphenylalanylleucine  
 11-18. N-phenylacetylphenylalanylleucine  
 11-19. N-benzyloxycarbonylphenylalanylleucine  
 11-20. N-benzoylhistidylleucine  
 11-21. N-(*p*-toluoyl)histidylleucine  
 15 11-22. N-(4-hydroxybenzoyl)histidylleucine  
 11-23. N-(1-naphthoyl)histidylleucine  
 11-24. N-benzoylglycylphenylalanylleucine  
 11-25. N-(4-methoxybenzoyl)glycylphenylalanylleucine  
 11-26. N-phenylacetylglycylphenylalanylleucine  
 20 11-27. N-*t*-butoxycarbonylleucine

## 12. Isoleucine derivatives.

- 25 12-1. N-valerylisoleucine  
 12-2. N-pivaloylisoleucine  
 12-3. N-octanoylisoleucine  
 12-4. N-benzoylisoleucine  
 12-5. N-(3-hydroxybenzoyl)isoleucine  
 30 12-6. N-cyclopentanecarbonylisoleucine  
 12-7. N-cyclohexanecarbonylisoleucine  
 12-8. N-(1-phenyl-1-cyclopentanecarbonyl)isoleucine  
 12-9. N-phenylacetylisoleucine  
 12-10. N-methoxycarbonylisoleucine  
 35 12-11. N-propoxycarbonylisoleucine  
 12-12. N-isopropoxycarbonylisoleucine  
 12-13. N-benzyloxycarbonylisoleucine

## 13. Norleucine derivatives.

- 13-1. N-propionylnorleucine  
 13-2. N-valerylnorleucine  
 13-3. N-pivaloylnorleucine  
 45 13-4. N-nonanoylnorleucine  
 13-5. N-benzoylnorleucine  
 13-6. N-(4-hydroxybenzyl)norleucine  
 13-7. N-cyclohexanecarbonylnorleucine  
 13-8. N-(1-phenyl-1-cyclopropanecarbonyl)norleucine  
 50 13-9. N-( $\alpha$ -phenyl- $\alpha$ -ethylacetyl)norleucine  
 13-10. N-ethoxycarbonylnorleucine  
 13-11. N-propoxycarbonylnorleucine  
 13-12. N-butoxycarbonylnorleucine  
 55 13-13. N-benzyloxycarbonylnorleucine

14. Oligopeptide derivatives

- 14-1. N-benzoylglycylphenylalanine  
 14-2. N-(4-hydroxybenzoyl)glycylphenylalanine  
 5 14-3. N-(1-naphthoyl)glycylphenylalanine  
 14-4. N-ethoxycarbonylglycylphenylalanine  
 14-5. N-benzyloxycarbonylglycylphenylalanine  
 14-6. N-benzoylalanylphenylalanine  
 14-7. N-(p-toluoyl)alanylphenylalanine  
 10 14-8. N-(4-hydroxybenzoyl)alanylphenylalanine  
 14-9. N-(4-aminobenzoyl)alanylphenylalanine  
 14-10. N-(1-naphthoyl)alanylphenylalanine  
 14-11. N-benzyloxycarbonylalanylphenylalanine  
 14-12. N-benzoylleucylphenylalanine  
 15 14-13. N-(4-hydroxybenzoyl)leucylphenylalanine  
 14-14. N-cyclohexanecarbonylleucylphenylalanine  
 14-15. N-benzyloxycarbonylleucylphenylalanine

20 15. Tyrosine derivatives.

- 15-1. N-benzoyltyrosine  
 15-2. N-(3-methoxybenzoyl)tyrosine  
 15-3. N-cyclohexanecarbonyltyrosine  
 25 15-4. N-benzyloxycarbonyltyrosine  
 15-5. N-phenethylloxycarbonyltyrosine

16. O-Methyltyrosine derivatives.

- 30 16-1. N-acetyl-O-methyltyrosine  
 16-2. N-propioloyl-O-methyltyrosine  
 16-3. N-benzoyl-O-methyltyrosine  
 16-4. N-(4-aminobenzoyl)-O-methyltyrosine  
 35 16-5. N-(1-phenyl-1-cyclopentanecarbonyl)-O-methyltyrosine  
 16-6. N-(1-phenyl-1-cyclohexanecarbonyl)-O-methyltyrosine  
 16-7. N-methoxycarbonyl-O-methyltyrosine  
 16-8. N-benzyloxycarbonyl-O-methyltyrosine  
 16-9. N-phenylethylloxycarbonyl-O-methyltyrosine  
 40

17. Aspartic acid derivatives.

- 17-1. N-heptanoylaspartic acid  
 45 17-2. N-decanoylaspartic acid  
 17-3. N-(4-hydroxybenzoyl)aspartic acid  
 17-4. N-(3-hydroxy-2-naphthoyl)aspartic acid  
 17-5. N-(1-phenyl-1-cyclopentanecarbonyl)aspartic acid  
 17-6. N-(1-phenyl-1-cyclohexanecarbonyl)aspartic acid  
 50 17-7. N-benzyloxycarbonylaspartic acid  
 17-8. N-(4-methoxybenzyloxycarbonyl)aspartic acid

18. Glutamic acid derivatives.

- 55 18-1. N-nonanoylglutamic acid  
 18-2. N-(4-methoxybenzoyl)glutamic acid  
 18-3. N-(1-naphthoyl)glutamic acid

- 18-4. N-(1-phenyl-1-cyclopentanecarbonyl)glutamic acid  
 18-5. N-benzyloxycarbonylglutamic acid  
 18-6. N-benzoylglutamic acid

5

19. 4-Carboxyglutamic acid derivatives.

- 19-1. N-heptanoyl-4-carboxyglutamic acid  
 19-2. N-(4-methoxybenzoyl)-4-carboxyglutamic acid  
 10 19-3. N-(1-naphthoyl)-4-carboxyglutamic acid  
 19-4. N-(1-hydroxy-2-naphthoyl)-4-carboxyglutamic acid  
 19-5. N-phenylacetyl-4-carboxyglutamic acid

15 20. 3-Methylaspartic acid derivatives.

- 20-1. N-octanoyl-3-methylaspartic acid  
 20-2. N-(4-methoxybenzoyl)-3-methylaspartic acid  
 20-3. N-( $\alpha$ -phenyl- $\alpha$ -cyclopentylacetyl)-3-methylaspartic acid  
 20

21. 2-Aminoadipic acid derivatives.

- 21-1. N-hexanoyl-2-aminoadipic acid  
 25 21-2. N-benzoyl-2-aminoadipic acid  
 21-3. N-(*p*-toluoyl)-2-aminoadipic acid  
 21-4. N-(1-naphthoyl)-2-aminoadipic acid  
 21-5. N-(4-phenylbutyryl)-2-aminoadipic acid  
 21-6. N-phenylacetyl-2-aminoadipic acid  
 30 21-7. N-ethoxycarbonyl-2-aminoadipic acid

22. 2-Aminopimelic acid derivatives.

- 22-1. N-valeryl-2-aminopimelic acid  
 35 22-2. N-benzoyl-2-aminopimelic acid  
 22-3. N-(3-phenylpropionyl)-2-aminopimelic acid  
 22-4. N-methoxycarbonyl-2-aminopimelic acid  
 22-5. N-ethoxycarbonyl-2-aminopimelic acid  
 40 22-6. N-benzyloxycarbonyl-2-aminopimelic acid

23. 2-Aminosuberic acid derivatives.

- 23-1. N-butyryl-2-aminosuberic acid  
 45 23-2. N-benzoyl-2-aminosuberic acid  
 23-2. N-(1-naphthoyl)-2-aminosuberic acid  
 23-4. N-( $\alpha$ -phenyl- $\alpha$ -cyclopentylacetyl)-2-aminosuberic acid  
 23-5. N-methoxycarbonyl-2-aminosuberic acid  
 50 23-6. N-propoxycarbonyl-2-aminosuberic acid

24. 3-Hydroxyaspartic acid derivatives.

- 24-1. N-(1-naphthoyl)-3-hydroxyaspartic acid  
 55 24-2. N-(1-phenyl-1-cyclohexanecarbonyl)-3-hydroxyaspartic acid

24-3. N-( $\alpha$ -phenyl- $\alpha$ -ethylacetyl)-3-hydroxyaspartic acid25. 3-Hydroxyglutamic acid derivatives.

5

- 25-1. N-(1-naphthoyl)-3-hydroxyglutamic acid  
 25-2. N-(1-phenyl-1-cyclohexanecarbonyl)-3-hydroxyglutamic acid  
 25-3. N-( $\alpha$ , $\alpha$ -diphenylacetyl)-3-hydroxyglutamic acid

10

26. 2,3-Diaminopropionic acid derivatives.

15

- 26-1. N $^{\alpha}$ -hexanoyl-2,3-diaminopropionic acid  
 26-2. N $^{\alpha}$ -(4-butylbenzoyl)-2,3-diaminopropionic acid  
 26-3. N $^{\alpha}$ ,N $^{\delta}$ -dibenzoyl-2,3-diaminopropionic acid  
 26-4. N $^{\alpha}$ -(1-phenyl-1-cyclopentanecarbonyl)-2,3-diaminopropionic acid  
 26-5. N $^{\alpha}$ -( $\alpha$ -phenyl- $\alpha$ -ethylacetyl)-2,3-diaminopropionic acid

27. 2,4-Diaminobutyric acid derivatives.

25

- 27-1. N $^{\alpha}$ -(1-naphthoyl)-2,4-diaminobutyric acid  
 27-2. N $^{\alpha}$ ,N $^{\gamma}$ -dibenzoyl-2,4-diaminobutyric acid  
 27-3. N $^{\alpha}$ -(1-phenyl-1-cyclopentanecarbonyl)-2,4-diaminobutyric acid  
 27-4. N $^{\alpha}$ -( $\alpha$ -phenyl- $\alpha$ -ethylacetyl)-2,4-diaminobutyric acid

28. 5-Hydroxylysine derivatives.

30

- 28-1. N $^{\alpha}$ -(p-toluoyl)-5-hydroxylysine  
 28-2. N $^{\alpha}$ ,N $^{\delta}$ -dibenzoyl-5-hydroxylysine  
 28-3. N $^{\alpha}$ -(1-phenyl-1-cyclopentanecarbonyl)-5-hydroxylysine  
 28-4. N $^{\alpha}$ -( $\alpha$ -phenyl- $\alpha$ -cyclopentylacetyl)-5-hydroxylysine  
 28-5. N $^{\alpha}$ -(1-phenyl-1-cyclopentanecarbonyl)-5-hydroxylysine

35

29. Arginine derivatives.

40

- 29-1. N $^{\alpha}$ -heptanoylarginine  
 29-2. N $^{\alpha}$ -(2-methoxybenzoyl)arginine

30. N $^{\delta}$ ,N $^{\delta}$ -Dimethylornithine derivatives.

45

- 30-1. N $^{\alpha}$ -pivaloyl-N $^{\delta}$ ,N $^{\delta}$ -dimethylornithine  
 30-2. N $^{\alpha}$ -octanoyl-N $^{\delta}$ ,N $^{\delta}$ -dimethylornithine  
 30-3. N $^{\alpha}$ -acryloyl-N $^{\delta}$ ,N $^{\delta}$ -dimethylornithine  
 30-4. N $^{\alpha}$ -benzoyl-N $^{\delta}$ ,N $^{\delta}$ -dimethylornithine  
 30-5. N $^{\alpha}$ -(4-hydroxybenzoyl)-N $^{\delta}$ ,N $^{\delta}$ -dimethylornithine  
 30-6. N $^{\alpha}$ -cyclohexanecarbonyl-N $^{\delta}$ ,N $^{\delta}$ -dimethylornithine  
 30-7. N $^{\alpha}$ -( $\alpha$ -phenyl- $\alpha$ -methylacetyl)-N $^{\delta}$ ,N $^{\delta}$ -dimethylornithine  
 30-8. N $^{\alpha}$ -ethoxycarbonyl-N $^{\alpha}$ ,N $^{\alpha}$ -dimethylornithine  
 30-9. N $^{\alpha}$ -butoxycarbonyl-N $^{\delta}$ ,N $^{\delta}$ -dimethylornithine  
 30-10. N $^{\alpha}$ -benzyloxycarbonyl-N $^{\delta}$ ,N $^{\delta}$ -dimethylornithine

55

31. N<sup>ε</sup>-Methyllysine derivatives.

- 31-1. N<sup>α</sup>-hexanoyl-N<sup>ε</sup>-methyllysine  
 31-2. N<sup>α</sup>-nonanoyl-N<sup>ε</sup>-methyllysine  
 5 31-3. N<sup>α</sup>-acryloyl-N<sup>ε</sup>-methyllysine  
 31-4. N<sup>α</sup>-benzoyl-N<sup>ε</sup>-methyllysine  
 31-5. N<sup>α</sup>-(4-butoxybenzoyl)-N<sup>ε</sup>-methyllysine  
 31-6. N<sup>α</sup>-(3-sulphobenzoyl)-N<sup>ε</sup>-methyllysine  
 10 31-7. N<sup>α</sup>-cyclobutanecarbonyl-N<sup>ε</sup>-methyllysine  
 31-8. N<sup>α</sup>-cyclohexanecarbonyl-N<sup>ε</sup>-methyllysine  
 31-9. N<sup>α</sup>-phenylacetyl-N<sup>ε</sup>-methyllysine  
 31-10. N<sup>α</sup>-propoxycarbonyl-N<sup>ε</sup>-methyllysine  
 31-11. N<sup>α</sup>-isopropoxycarbonyl-N<sup>ε</sup>-methyllysine  
 31-12. N<sup>α</sup>-benzyloxycarbonyl-N<sup>ε</sup>-methyllysine

32. Cysteine derivatives.

- 32-1. N-phenylacetylcysteine

33. Methionine derivatives.

- 33-1. N-valerylmethionine  
 25 33-2. N-acryloylmethionine  
 33-3. N-methacryloylmethionine  
 33-4. N-benzoylmethionine  
 33-5. N-(p-toluoyl)methionine  
 33-6. N-(4-methoxybenzoyl)methionine  
 30 33-7. N-(4-aminobenzoyl)methionine  
 33-8. N-cyclopentanecarbonylmethionine  
 33-9. N-cyclohexanecarbonylmethionine  
 33-10. N-(1-phenyl-1-cyclohexanecarbonyl)methionine  
 33-11. N-phenylacetylmethionine  
 35 33-12. N-(α-phenyl-α-methylacetyl)methionine  
 33-13. N-methoxycarbonylmethionine  
 33-14. N-ethoxycarbonylmethionine  
 33-15. N-butoxycarbonylmethionine  
 33-16. N-benzyloxycarbonylmethionine  
 40 33-17. N-(4-methylbenzyloxycarbonyl)methionine  
 33-18. N-benzoylglycylmethionine  
 33-19. N-(4-methoxybenzoyl)glycylmethionine  
 33-20. N-benzyloxycarbonylglycylmethionine  
 33-21. N-benzoylvalylmethionine  
 45 33-22. N-cyclopentanecarbonylvalylmethionine  
 33-23. N-ethoxycarbonylvalylmethionine

34. Ethionine derivatives.

- 34-1. N-butyrylethionine  
 34-2. N-benzoylethionine  
 34-3. N-(p-toluoyl)ethionine  
 34-4. N-(m-toluoyl)ethionine  
 50 34-5. N-(4-butylbenzoyl)ethionine  
 34-6. N-(4-hydroxybenzoyl)ethionine  
 34-7. N-(4-aminobenzoyl)ethionine  
 34-8. N-(3-sulphobenzoyl)ethionine

- 34-9. N-(1-phenyl-1-cyclopropanecarbonyl)ethionine  
 34-10. N -phenylacetylthionine  
 34-11. N-methoxycarbonylthionine  
 34-12. N-ethoxycarbonylthionine  
 5 34-13. N-benzyloxycarbonylthionine  
 34-14. N-(4-methoxybenzyloxycarbonyl)ethionine  
 34-15. N-cyclohexanecarbonylthionine

10 35. S-Carboxymethylcysteine derivatives.

- 35-1. N-propionyl-S-carboxymethylcysteine  
 35-2. N-acryloyl-S-carboxymethylcysteine  
 35-3. N-benzoyl-S-carboxymethylcysteine  
 15 35-4. N-(p-toluoyl)-S-carboxymethylcysteine  
 35-5. N-(4-methoxybenzoyl)-S-carboxymethylcysteine  
 35-6. N-(4-butoxybenzoyl)-S-carboxymethylcysteine  
 35-7. N-cyclohexanecarbonyl-S-carboxymethylcysteine  
 35-8. N-(1-phenyl-1-cyclopentanecarbonyl)-S-carboxymethylcysteine  
 20 35-9. N-( $\alpha$ -methylbenzyloxycarbonyl)-S -carboxymethylcysteine

36. S-Benzylcysteine derivatives.

- 25 36-1. N -benzoyl-S-benzylcysteine  
 36-2. N -(4-hydroxybenzoyl)-S-benzylcysteine  
 36-3. N-(3-sulphobenzoyl)-S-benzylcysteine  
 36-4. N-cyclopropanecarbonyl-S-benzylcysteine  
 36-5. N-methoxycarbonyl-S -benzylcysteine  
 30 36-6. N-ethoxycarbonyl-S-benzylcysteine  
 36-7. N-propoxycarbonyl-S-benzylcysteine  
 36-8. N -(4-hydroxybenzyloxycarbonyl)-S-benzylcysteine

35 37. Methionine S-oxide derivatives.

- 37-1. N-(p-toluoyl)methionine S-oxide  
 37-2. N-pentyloxycarbonylmethionine S-oxide  
 37-3. N-benzyloxycarbonylmethionine S-oxide  
 40

38. Ethionine S-oxide derivatives.

- 38-1. N-benzoylethionine S-oxide  
 45 38-2. N-benzyloxycarbonylethionine S-oxide

39. Methionine S,S-dioxide derivatives.

- 50 39-1. N-(1-naphthoyl)methionineS, S-dioxide  
 39-2. N-cyclohexanecarbonylmethionine S,S-dioxide  
 39-3. N-pentyloxycarbonylmethionine S, S-dioxide

55 40. Cysteic acid derivatives.

- 40-1. N-(p-toluoyl)cysteic acid  
 40-2. n-(1-naphthoyl)cysteic acid

- 40-3. N-(3-hydroxy-2-naphthoyl)cysteic acid  
 40-4. N-(1-phenyl-1-cyclohexanecarbonyl)cysteic acid

5 41. Serine derivatives.

- 41-1. N-octanoylserine  
 41-2. N-benzoylserine  
 41-3. N-(m-toluoyl)serine  
 10 41-4. N-(4-methoxybenzoyl)serine  
 41-5. N-(1-naphthoyl)serine  
 41-6. N-(1-phenyl-1-cyclopentanecarbonyl)serine  
 41-7. N-benzyloxycarbonylserine  
 41-8. N-( $\alpha$ -methylbenzyloxycarbonyl)serine

15

42. O-methylserine derivatives.

- 42-1. N-valeryl-O-methylserine  
 20 42-2. N-benzoyl-O-methylserine  
 42-3. N-cyclohexanecarbonyl-O-methylserine  
 42-4. N-phenylacetyl-O-methylserine  
 42-5. N-( $\alpha$ -phenyl- $\alpha$ -methylacetyl)-O-methylserine  
 42-6. N-(3-phenylpropionyl)-O-methylserine  
 25 42-7. N-phenethyloxycarbonyl-O-methylserine

43. Threonine derivatives.

- 30 43-1. N-hexanoylthreonine  
 43-2. N-nonanoylthreonine  
 43-3. N-benzoylthreonine  
 43-4. N-(3-hydroxy-2-naphthoyl)threonine  
 43-5. N-cyclohexanecarbonylthreonine  
 35 43-6. N-( $\alpha$ , $\alpha$ -diphenylacetyl)threonine  
 43-7. N-butoxycarbonylthreonine  
 43-8. N-benzyloxycarbonylthreonine  
 43-9. N-(4-methoxybenzyloxycarbonyl)threonine

40

44. O-Methylthreonine derivatives.

- 44-1. N -butyryl-O-methylthreonine  
 44-2. N -(4-methoxybenzyoyl)-O-methylthreonine  
 45 44-3. N-(1-naphthoyl)-O-methylthreonine  
 44-4. N-(1-phenyl-1-cyclopentanecarbonyl)-O-methylthreonine  
 44-5. N-ethyoxycarbonyl-O -methylthreonine  
 44-6. N-(3-phenylpropoxycarbonyl)-O-methylthreonine

50

45. Homoserine derivatives.

- 45-1. N-heptanoylhomoserine  
 45-2. N-benzoylhomoserine  
 55 45-3. N-(3-methoxybenzoyl)homoserine  
 45-4. N-( $\alpha$ -phenyl- $\alpha$ -cyclopentylacetyl)homoserine  
 45-5. N -(4-hydroxybenzyloxycarbonyl)homoserine



45-6. N -(4-methylbenzyloxycarbonyl)homoserine46. Ethoxinine derivatives.

5

- 46-1. N-benzoylethoxinine
- 46-2. N-(4-butoxybenzoyl)ethoxine
- 46-3. N-cyclohexanecarbonylethoxinine
- 46-4. N-methoxycarbonylethoxinine

10

47. 3-Methoxyvaline derivatives.

15

- 47-1. N-isovaleryl-3-methoxyvaline
- 47-2. N-(p-toluoyl)-3-methoxyvaline
- 47-3. N-(1-naphthoyl)-3-methoxyvaline
- 47-4. N-cyclopentanecarbonyl-3-methoxyvaline
- 47-5. N-cyclohexanecarbonyl-3-methoxyvaline
- 47-6. N-methoxycarbonyl-3-methoxyvaline
- 47-7. N-ethoxycarbonyl-3-methoxyvaline

20

48. 3-Phenylserine derivatives.

25

- 48-1. N-propionyl-3-phenylserine
- 48-2. N-(4-aminobenzoyl)-3-phenylserine
- 48-3. N-(1-naphthoyl)-3-phenylserine
- 48-4. N-benzoyl-3-phenylserine
- 48-5. N-cyclohexanecarbonyl-3-phenylserine
- 48-6. N-phenylacetyl-3-phenylserine
- 48-7. N-methoxycarbonyl-3-phenylserine
- 48-8. N-butoxycarbonyl-3-phenylserine
- 48-9. N-benzyloxycarbonyl-3-phenylserine
- 48-10. N-( $\alpha$ -methylbenzyloxycarbonyl)-3-phenylserine

30

35

49. 3-Methyl-3-phenylalanine derivatives.

40

- 49-1. N-acetyl-3-methyl-3-phenylalanine
- 49-2. N-hexanoyl-3-methyl-3-phenylalanine
- 49-3. N-benzoyl-3-methyl-3-phenylalanine
- 49-4. N-(4-aminobenzoyl)-3-methyl-3-phenylalanine
- 49-5. N-(3-sulphobenzoyl)-3-methyl-3-phenylalanine
- 49-6. N-cyclobutanecarbonyl-3-methyl-3-phenylalanine
- 49-7. N-cyclopentanecarbonyl-3-methyl-3-phenylalanine
- 49-8. N-phenylacetyl-3-methyl-3-phenylalanine
- 49-9. N-isopropoxycarbonyl-3-methyl-3-phenylalanine
- 49-10. N-butoxycarbonyl-3-methyl-3-phenylalanine
- 49-11. N-(4-aminobenzyloxycarbonyl)-3-methyl-3-phenylalanine

45

50

50. Histidine derivatives.

55

- 50-1. N-acetylhistidine
- 50-2. N-hexanoylhistidine
- 50-3. N-acryloylhistidine
- 50-4. N-methacryloylhistidine
- 50-5. N-benzoylhistidine

- 50-6. N-(p-toluoyl)histidine  
 50-7. N-(4-methoxybenzoyl)histidine  
 50-8. N-(4-butoxybenzoyl)histidine  
 50-9. N-cyclopentanecarbonylhistidine  
 5 50-10. N-cyclohexanecarbonylhistidine  
 50-11. N-(1-phenyl-1-cyclopentanecarbonyl)histidine  
 50-12. N-phenylacetylhistidine  
 50-13. N-( $\alpha$ -phenyl- $\alpha$ -cyclopentylacetyl)histidine  
 50-14. N-(4-methoxybenzyloxycarbonyl)histidine  
 10 50-15. N-benzoylglycylhistidine  
 50-16. N-(4-butylbenzoyl)glycylhistidine  
 50-17. N-phenylacetylglycylhistidine  
 50-18. N-ethoxycarbonylglycylhistidine  
 50-19. N-benzyloxycarbonylglycylhistidine  
 15 50-20. N-benzoylglycylglycylhistidine  
 50-21. N-ethoxycarbonylglycylglycylhistidine  
 50-22. N-benzyloxycarbonylglycylglycylhistidine  
 50-23. N-t-butoxycarbonylhistidine

20

51. Tryptophan derivatives.

- 51-1. N-(4-hydroxybenzoyl)tryptophan  
 51-2. N-benzyloxycarbonyltryptophan

25

52. 2-Methylalanine derivatives.

- 52-1. N-propionyl-2-methylalanine  
 30 52-2. N-benzoyl-2-methylalanine  
 52-3. N-(m-toluoyl)-2-methylalanine  
 52-4. N-(3-methoxybenzoyl)-2-methylalanine  
 52-5. N-cyclobutanecarbonyl-2-methylalanine  
 52-6. N-phenylacetyl-2-methylalanine  
 35 52-7. N-phenethylloxycarbonyl-2-methylalanine

53. 2-Methylserine derivatives.

- 53-1. N-valeryl-2-methylserine  
 40 53-2. N-octanoyl-2-methylserine  
 53-3. N-benzoyl-2-methylserine  
 53-4. N-(p-toluoyl)-2-methylserine  
 53-5. N-(4-methoxybenzoyl)-2-methylserine  
 45 53-6. N-(1-naphthoyl)-2-methylserine  
 53-7. N-cyclopentanecarbonyl-2-methylserine  
 53-8. N-( $\alpha,\alpha$ -diphenylacetyl)-2-methylserine  
 53-9. N-pentylloxycarbonyl-2-methylserine

50

54. 2-Hydroxyisoleucine derivatives.

- 54-1. N-valeryl-2-hydroxyisoleucine  
 54-2. N-heptanoyl-2-hydroxyisoleucine  
 55 54-3. N-benzoyl-2-hydroxyisoleucine  
 54-4. N-(4-butylbenzoyl)-2-hydroxyisoleucine  
 54-5. N-(3-hydroxy-2-naphthoyl)-2-hydroxyisoleucine  
 54-6. N-cyclohexanecarbonyl-2-hydroxyisoleucine

54-7. N -phenylacetyl-2-hydroxyisoleucine55. 2-Methylmethionine derivatives.

5

- 55-1. N -hexanoyl-2-methylmethionine
- 55-2. N-benzoyl-2-methylmethionine
- 55-3. N-(4-hydroxybenzoyl)-2-methylmethionine
- 55-4. N-propoxycarbonyl-2-methylmethionine
- 10 55-5. N -isopropoxycarbonyl-2-methylmethionine

56. 2-Ethyl-2-phenylglycine derivatives.

15

- 56-1. N-acetyl-2-ethyl-2-phenylglycine
- 56-2. N-butyryl-2-ethyl-2-phenylglycine
- 56-3. N-(3-sulphobenzoyl)-2-ethyl-2-phenylglycine
- 56-4. N-ethoxycarbonyl-2-ethyl-2-phenylglycine
- 20 56-5. N-propoxycarbonyl-2-ethyl-2-phenylglycine

57. 3-Aminobutyric acid derivatives.

25

- 57-1. N -hexanoyl-3-aminobutyric acid
- 57-2. N-benzoyl-3-aminobutyric acid
- 57-3. N-(4-methoxybenzoyl)-3-aminobutyric acid
- 57-4. N-(3-sulphobenzoyl)-3-aminobutyric acid
- 57-5. N-(1-naphthoyl)-3-aminobutyric acid
- 57-6. N-cyclopropanecarbonyl-3-aminobutyric acid
- 30 57-7. N-( $\alpha,\alpha$ -diphenylacetyl)-3-aminobutyric acid
- 57-8. N -(4-phenylbutyl)-3-aminobutyric acid
- 57-9. N -( $\alpha$ -methylbenzyloxycarbonyl)-3-aminobutyric acid

35 58. 3-Amino-4-methylvaleric acid derivatives.

40

- 58-1. N-valeryl-3-amino-4-methylvaleric acid
- 58-2. N-isovaleryl-3-amino-4-methylvaleric acid
- 58-3. N-heptanoyl-3-amino-4-methylvaleric acid
- 58-4. N-benzoyl-3-amino-4-methylvaleric acid
- 58-5. N-(*m*-toluoyl)-3-amino-4-methylvaleric acid
- 58-6. N-(3-sulphobenzoyl)-3-amino-4-methylvaleric acid
- 58-7. N-(1-naphthoyl)-3-amino-4-methylvaleric acid
- 58-8. N-phenylacetyl-3-amino-4-methylvaleric acid
- 45 58-9. N-(3-phenylpropionyl)-3-amino-4-methylvaleric acid
- 58-10. N-butoxycarbonyl-3-amino-4-methylvaleric acid
- 58-11. N-(4-methylbenzyloxycarbonyl)-3-amino-4-methylvaleric acid

50 59. 3-Amino-3-phenylpropionic acid derivatives.

55

- 59-1. N-butyryl-3-amino-3-phenylpropionic acid
- 59-2. N-valeryl-3-amino-3-phenylpropionic acid
- 59-3. N-benzoyl-3-amino-3-phenylpropionic acid
- 59-4. N-(4-aminobenzoyl)-3-amino-3-phenylpropionic acid
- 59-5. N-cyclopropanecarbonyl-3-amino-3-phenylpropionic acid
- 59-6. N-cyclobutanecarbonyl-3-amino-3-phenylpropionic acid
- 59-7. N-cyclopentanecarbonyl-3-amino-3-phenylpropionic acid

- 59-8. N-methoxycarbonyl-3-amino-3-phenylpropionic acid  
 59-9. N-propoxycarbonyl-3-amino-3-phenylpropionic acid  
 59-10. N-butoxycarbonyl-3-amino-3-phenylpropionic acid  
 59-11. N-(4-aminobenzoyloxycarbonyl)-3-amino-3-phenylpropionic acid

5

60. 3-Amino-2-hydroxypropionic acid derivatives.

- 60-1. N-valeryl-3-amino-2-hydroxypropionic acid  
 10 60-2. N-heptanoyl-3-amino-2-hydroxypropionic acid  
 60-3. N-benzoyl-3-amino-2-hydroxypropionic acid  
 60-4. N-(3-methoxybenzoyl)-3-amino-2-hydroxypropionic acid  
 60-5. N-cyclohexanecarbonyl-3-amino-2-hydroxypropionic acid  
 60-6. N-benzyloxycarbonyl-3-amino-2-hydroxypropionic acid  
 15 60-7. N-(3-phenylpropoxycarbonyl)-3-amino-2-hydroxypropionic acid

61. 4-Amino-3-hydroxybutyric acid derivatives

- 61-1. N-isobutyryl-4-amino-3-hydroxybutyric acid  
 20 61-2. N-decanoyl-4-amino-3-hydroxybutyric acid  
 61-3. N-benzoyl-4-amino-3-hydroxybutyric acid  
 61-4. N-(*o*-toluoyl)-4-amino-3-hydroxybutyric acid  
 61-5. N-(3-aminobenzoyl)-4-amino-3-hydroxybutyric acid  
 25 61-6. N-(1-phenyl-1-cyclohexanecarbonyl)-4-amino-3-hydroxybutyric acid  
 61-7. N-( $\alpha$ -phenyl- $\alpha$ -methylacetyl)-4-amino-3-hydroxybutyric acid  
 61-8. N-(4-methoxybenzyloxycarbonyl)-4-amino-3-hydroxybutyric acid

Of the amino acid derivatives listed above, the following are particularly preferred: Compounds No. 2-5, 2-6, 2-7, 2-18, 2-22, 4-6, 5-11, 5-18, 5-33, 6-3, 7-3, 7-5, 7-14, 8-4, 9-3, 10-4, 10-29, 10-45, 11-3, 11-24, 13-5, 14-1, 14-6, 14-14, 16-3, 33-4, 33-11, 33-21, 34-2, 34-14, 43-3, 50-5, 50-6, 50-7, 57-3 and 59-1. Of these, 30 Compounds No. 2-22 and 10-45, especially No. 2-22, are most preferred.

The amino acid derivatives employed in the present invention are acids and, as such, are capable of forming salts; any pharmaceutically acceptable salt of these amino acids may be employed. Examples of such salts include: alkali metal salts such as the sodium or potassium salts; alkaline earth metal salts, such as the calcium salt; other metal salts, such as the magnesium, aluminium, iron, zinc, copper, nickel and 35 cobalt salts; the ammonium salt; and salts with amino sugars, such as glucosamine and galactosamine.

The compositions of the invention may be prepared by any suitable method which involves mixing the antibiotic with the amino acid derivative and the invention is not intended to be limited by any particular method of preparation. Since the amino acid derivatives employed in this invention have, in general, very 40 limited solubility in water, it is preferred that they should first be dispersed in water and then converted to a suitable salt by adding an aqueous solution of an appropriate base, for example: a metal compound, such as sodium hydroxide or potassium hydroxide; ammonia; or an amino sugar, such as glucosamine or galactosamine. Sufficient of the base is preferably added to adjust the pH of the mixture to a value within the range from 5.5 to 9, more preferably from 6 to 9.

45 The penem or carbapenem antibiotic is then added to the resulting solution. The mixed solution thus obtained may be employed as such or it may first be lyophilized to give a powdery mixture, which may be subsequently formulated into an appropriate dosage form suitable for the chosen route of administration, either by the manufacturer or prior to use.

The above mixing and preparation steps may take place at any temperature at which the components are fluid (especially the media) and are not decomposed, e.g. from 0 to 100°C, more conveniently from 0 to 50°C and most conveniently at about ambient temperature.

Although it is convenient to administer the antibiotic and the amino acid derivative simultaneously in a single composition, it is, of course, clear that the two compounds may be administered separately, provided that they are administered sufficiently closely in time to each other that the amino acid derivative has a 55 suitable concentration in the blood for all or most of the time that the antibiotic is present. Normally, it is anticipated that this will be achieved if the two compounds are administered within about one hour of each other, the amino acid preferably being administered before the antibiotic.

The composition of the invention is particularly suitable for use by intravenous administration.

There is no particular restriction on the relative proportions of the amino acid derivative and the penem or carbapenem antibiotic; in general, we have found that weight proportions of amino acid derivative to antibiotic of from 0.1:1 to 4:1 give good results, but equally proportions outside this range may successfully be employed. Approximately equal weights are generally most convenient.

5 The invention is further illustrated by the following Examples and Activity Tests. In the following, the penem or carbapenem antibiotics are referred to by the numbers appended to them in the foregoing list and are identified as "(Carba)-Penem Cpd No" whilst the amino acid derivatives are also identified by the numbers appended to them in the foregoing list and are referred to as "Amino Acid Cpd No."

10

#### EXAMPLE 1

5 g of N-benzoylvaline (Amino Acid Compound No. 10-45) were weighed out and dispersed in 80 ml of water. A 1N aqueous solution of sodium hydroxide was slowly added to this dispersion, and dissolved the N-benzoylvaline when the pH of the solution reached a value of 7-8. Then, 5 g of (5R,6S)-2-[(3S)-1-acetimidopyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid (Carbapenem Compound No. 6) were dissolved in this solution, to give a total volume of 100 ml.

#### 20 EXAMPLE 2

5 g of N-benzoyl- $\beta$ -alanine (Amino Acid Compound No. 2-22) were weighed out and dispersed in 40 ml of water. A 1N aqueous solution of sodium hydroxide was slowly added to this dispersion, and dissolved the N-benzoyl- $\beta$ -alanine when the pH of the solution reached a value of 7-8. Then, 5 g of (5R,6S)-2-[(3S)-1-acetimidopyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid (Carbapenem Compound No. 6) were dissolved in this solution, to give a total volume of 50 ml.

#### 30 EXAMPLE 3

Similar procedures to those described in Examples 1 and 2 were carried out, using the other penem or carbapenem antibiotic substances and the other acylated amino acid derivatives shown in the following Table, in the amounts shown in that Table.

In this Table, where the amino acid derivatives are not specified as being D- or L-, then they are the DL-form.

#### ACTIVITY TESTS

40 The preparation obtained by the procedure described in Example 1 was injected into the ear vein of a rabbit (about 3 kg body weight) in an amount of 3 ml/kg [that is 150 mg/kg of the Carbapenem Compound No. 6 + 150 mg/kg of N-benzoylvaline (Amino Acid Compound No. 10-45)]. A preparation which had been obtained by the same procedure as that described in Example 1 but not including the N-benzoylvaline was injected into another rabbit, as a control, in a similar manner to the above.

45 After one week, the kidneys of both rabbits were excised and examined. A change was observed in the renal tissue of the rabbits to which had been administered the preparation without the N-benzoylvaline, but no such change at all was observed in the renal tissue of rabbits to which had been administered the preparation containing the N-benzoylvaline.

50 Similar experiments were carried out on other preparations which were prepared from other penem or carbapenem antibiotic substances and other amino acid derivatives. The Table also shows the results of these experiments.

The observed change in the renal tissue of the control rabbits was a degenerative necrosis of the proximal renal tubules in the region of the renal cortex. In the following Table, where the proportion of the total area of this region which exhibited such necrosis was from 0 to 25%, this is shown as + + +. Where the area is less than 50% this is shown as + + and where it is less than 75% this is shown as +. Where different animals within each test group exhibited different responses, this is shown as e.g. + + + - + + or + + - +.

It should be noted that, whenever penem or carbapenem antibiotic substances which were not combined with amino acid derivatives were administered, a change in the renal tissue was observed. Hence, all of the experiments carried out (even where the effect is only "+") demonstrated a significant protective effect of the amino acid derivative.

5

10

Table

	(Carba)- Penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
15					
20	6	150	1-5	150	+
25	6	150	1-8	150	++
	6	150	1-10	150	+
	6	150	1-11	150	++
30	6	150	1-12	150	+
	6	150	2-3	150	++
35	6	150	2-4	150	++
	6	150	2-5	150	+++
	6	250	2-6	250	+++
40	6	150	2-7	150	+++
	6	150	2-10	150	++
45	6	150	2-11	150	++
	6	150	2-13	150	++
	6	150	2-14	150	++
50	6	150	2-15	150	++

55

Table (cont)

	(Carba)- penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
5					
10					
15	6	250	2-18	250	+++
	6	150	2-22	150	+++
	6	200	2-22	200	+++
20	6	300	2-22	300	+++
	6	300	2-22	150	++
25	6	400	3-3	400	+++
	6	150	3-6	150	+
	6	150	3-8	150	+
30	6	150	3-15	150	+
	6	150	4-1	150	+
35	6	150	4-4	150	+
	6	150	4-5	150	++
	5	150	4-6	150	+++
40	6	150	5-3	150	++
	6	150	5-11	150	++
45	6	150	5-14	150	+
	6	250	5-18	250	++
	6	150	5-33	150	+++
50	6	150	6-2	150	++
	6	150	6-3	150	+++
55	6	150	6-11	150	++
	6	150	7-2	150	+

Table (cont)

5					
	(Carba)-	Amount	Amino	Amount	Effect
	Penem	mg/kg	Acid	mg/kg	
10	Cpd. No.		Cpd. No.		
15	6	150	7-3	150	+++
	6	150	7-5	150	+++
	6	150	7-12	150	++
20	6	150	7-18	150	++
	6	150	8-2	150	+
25	6	150	8-4	150	+++
	6	150	8-8	150	++
	6	150	8-10	150	+
30	6	150	9-3	150	+++
	6	150	9-5	150	+
35	6	150	10-4	150	+++
	6	250	10-19	250	++
	6	150	10-24	150	+
40	6	150	10-30	150	+
	6	150	10-32	150	+
45	6	150	10-33	150	+
	6	150	10-34	150	++
	6	150	10-35	150	++
50	6	150	10-45	150	+++
	6	400	10-45	400	+++
55	6	400	10-45	200	++
	6	150	11-3	150	+++



Table (cont)

5					
	(Carba)-	Amount	Amino	Amount	Effect
10	Penem	mg/kg	Acid	mg/kg	
	Cpd. No.		Cpd. No.		
15	6	150	11-6	150	+
	6	150	11-7	150	+
20	6	150	11-8	150	+
	6	150	11-24	150	+++
	6	150	12-1	150	++
25	6	150	12-4	150	++
	6	150	13-1	150	++
30	6	150	13-2	150	++
	6	150	13-5	150	+++
	6	150	13-12	150	+
35	6	150	14-6	150	+++
	6	150	14-7	150	+
40	6	150	14-8	150	++
	6	150	14-9	150	+
	6	150	14-11	150	+
45	6	150	14-14	150	+++
	6	150	15-1	150	+
50	6	150	16-3	150	+++
	6	150	17-1	150	++
	6	150	17-3	150	+
55	6	150	17-8	150	+

Table (cont.)

	(Carba)- Penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
5					
10					
15	6	150	18-2	150	+
	6	150	19-2	150	+
20	6	150	19-3	150	+
	6	150	21-4	150	+
	6	150	22-6	150	+
25	6	150	23-3	150	++
	6	150	24-2	150	++
30	6	150	25-2	150	+
	6	150	26-1	150	+
	6	150	27-3	150	+
35	6	150	30-9	150	+
	6	150	31-5	150	+
40	6	400	33-4	400	+++
	6	150	33-5	150	++
	6	150	33-7	150	+
45	6	150	33-11	150	+++
	6	150	33-14	150	++
50	6	150	33-15	150	+
	6	150	33-16	150	+
	6	150	33-20	150	++
55	6	150	34-2	150	+++

Table (cont)

5					
	(Carba)-	Amount	Amino	Amount	Effect
10	Penem	mg/kg	Acid	mg/kg	
	Cpd. No.		Cpd. No.		
15	6	150	34-3	150	++
	6	150	34-6	150	+
20	6	150	34-8	150	+
	6	150	34-12	150	++
	6	150	34-13	150	++
25	6	150	34-14	150	+++
	6	150	35-3	150	+
30	6	150	36-3	150	++
	6	150	37-3	150	++
	6	150	39-2	150	++
35	6	150	41-2	150	+
	6	150	41-4	150	++
40	6	150	41-7	150	+
	6	150	42-2	150	++
	6	150	43-1	150	+
45	6	150	43-3	150	+++
	6	150	43-5	150	+
50	6	150	43-7	150	++
	6	150	43-8	150	++
	6	150	44-3	150	++
55	6	150	45-5	150	+

Table (cont)

5					
	(Carba)-	Amount	Amino	Amount	Effect
	Penem	mg/kg	Acid	mg/kg	
10	Cpd. No.		Cpd. No.		
15	6	150	46-1	150	++
	6	150	47-3	150	++
20	6	150	48-2	150	+
	6	150	48-5	150	++
	6	150	48-9	150	+
25	6	150	49-2	150	+
	6	150	49-7	150	+
30	6	400	50-5	400	+++
	6	150	50-6	150	+++
	6	150	50-7	150	+++
35	6	150	50-10	150	++
	6	150	50-12	150	++
40	6	150	51-1	150	++
	6	150	52-6	150	++
	6	150	53-1	150	++
45	6	150	54-1	150	++
	6	150	55-3	150	++
50	6	150	56-3	150	++
	6	150	57-3	150	+++
	6	150	57-4	150	++
55	6	150	57-6	150	+

Table (cont)

	(Carba)- Penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
5					
10					
15	6	150	57-7	150	+
	6	150	58-1	150	+
20	6	150	58-3	150	++
	6	150	58-6	150	+
	6	150	58-9	150	+
25	6	150	59-1	150	+++
	6	150	59-4	150	++
30	6	150	59-7	150	++
	6	150	60-2	150	+
	6	150	60-6	150	+
35	6	150	61-2	150	++
	1	150	2-22	150	++
40	1	150	3-3	150	++
	1	250	5-11	250	+++
	1	150	5-18	150	+++
45	1	150	10-45	150	++
	1	150	14-6	150	+++
50	1	150	33-4	150	+++
	1	150	34-10	150	++
	1	150	50-5	150	++
55	2	150	4-6	150	+++

Table (cont)

5					
	(Carba)-	Amount	Amino	Amount	Effect
10	Penem	mg/kg	Acid	mg/kg	
	Cpd. No.		Cpd. No.		
15	2	150	5-11	150	+++
	2	150	7-14	150	+++
20	2	250	9-3	250	+++
	2	150	10-23	150	++
	2	150	33-15	150	++
25	2	250	50-5	250	++
	2	150	50-23	150	++
30	3	150	5-11	150	+++
	3	250	10-29	250	+++
	3	250	13-5	250	++
35	3	150	13-13	150	++
	3	150	33-20	150	++
40	3	250	34-2	250	++
	3	150	50-12	150	++
	7	150	2-22	150	+++
45	7	250	5-11	250	++
	7	150	10-45	150	+++
50	7	150	14-1	150	+++
	7	150	50-6	150	+++
	8	150	2-22	150	++
55	8	150	6-11	150	+---

5

Table (cont)

10

(Carba)- Penem Cpd. No.	Amount mg/kg	Amino Acid Cpd. No.	Amount mg/kg	Effect
-------------------------------	-----------------	---------------------------	-----------------	--------

15

20

8	250	50-5	250	++-+++
---	-----	------	-----	--------

9	150	33-6	150	+
---	-----	------	-----	---

9	250	50-5	250	++
---	-----	------	-----	----

25

10	150	13-5	150	++
----	-----	------	-----	----

10	150	18-6	150	+
----	-----	------	-----	---

30

11	150	2-22	150	++
----	-----	------	-----	----

15	150	10-45	150	+++
----	-----	-------	-----	-----

19	150	<u>L</u> -10-45	150	++
----	-----	-----------------	-----	----

35

22	250	33-4	250	++
----	-----	------	-----	----

22	150	34-15	150	+---+
----	-----	-------	-----	-------

40

23	150	2-22	150	+++
----	-----	------	-----	-----

24	150	2-22	150	+++
----	-----	------	-----	-----

24	150	10-45	150	+++
----	-----	-------	-----	-----

45

24	150	<u>D</u> -10-45	150	+++
----	-----	-----------------	-----	-----

24	150	<u>L</u> -10-45	150	+++
----	-----	-----------------	-----	-----

50

24	150	18-5	150	+
----	-----	------	-----	---

25	150	9-3	150	++
----	-----	-----	-----	----

55

Table (cont)

5	(Carba)-	Amount	Amino	Amount	Effect
	Penem	mg/kg	Acid	mg/kg	
10	Cpd. No.		Cpd. No.		
15	28	150	3-18	150	+
	28	150	33-21	150	+++
	32	150	2-22	150	++
20	38	150	2-22	150	+++
	39	150	10-45	150	++
25	40	150	2-22	150	+++
	66	250	3-3	250	++
	67	150	5-19	150	++
30	67	150	12-4	150	+--+
	71	250	2-18	250	+++
35	71	250	5-21	250	++
	73	150	11-27	150	+
	73	150	34-10	150	++
40	75	150	14-6	150	++
	75	150	33-9	150	++

45 **Claims**

1. A composition comprising:  
 a penem or carbapenem antibiotic; and  
 a pharmaceutically acceptable N-acylated derivative of an amino acid wherein the amino group and the  
 50 carboxylic acid group are attached to a saturated aliphatic carbon chain or carbon atom, or a salt thereof,  
 provided that the amino acid is not ornithine, lysine, phenylalanine or phenylglycine alone.
2. A composition as claimed in Claim 1, wherein said amino acid is a compound of formula (II):  

$$\text{H}_2\text{N-X-COOH (II)}$$
 55 wherein X represents a  $\text{C}_1\text{-C}_{10}$  alkylene group or a  $\text{C}_1\text{-C}_{10}$  alkylene group having at least one substituent  
 selected from hydroxy groups,  $\text{C}_1\text{-C}_4$  alkoxy groups,  $\text{C}_6\text{-C}_{10}$  aryloxy groups, substituted  $\text{C}_6\text{-C}_{10}$  aryloxy  
 groups,  $\text{C}_7\text{-C}_9$  aralkyloxy groups, substituted  $\text{C}_7\text{-C}_9$  aralkyloxy groups, mercapto groups,  $\text{C}_1\text{-C}_4$  alkylthio  
 groups,  $\text{C}_6\text{-C}_{10}$  arylthio groups, substituted  $\text{C}_6\text{-C}_{10}$  arylthio groups,  $\text{C}_7\text{-C}_9$  aralkylthio groups, substituted  $\text{C}_7\text{-C}_9$



aralkylthio groups, C<sub>2</sub>-C<sub>6</sub> carboxyalkylthio groups, amino groups, amino groups having one or two substituents selected from:

C<sub>1</sub>-C<sub>4</sub> alkyl groups, C<sub>6</sub>-C<sub>10</sub> aryl groups, substituted C<sub>6</sub>-C<sub>10</sub> aryl groups, C<sub>7</sub>-C<sub>8</sub> aralkyl groups, substituted C<sub>7</sub>-C<sub>8</sub> aralkyl groups and carboxylic acyl groups,

5 C<sub>6</sub>-C<sub>10</sub> aryl groups, substituted C<sub>6</sub>-C<sub>10</sub> aryl groups, carboxy groups, amidino groups, sulpho groups, C<sub>1</sub>-C<sub>4</sub> alkylsulphinyl groups, C<sub>1</sub>-C<sub>4</sub>

alkylsulphonyl groups and heterocyclic groups having from 5 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, said substituted aryloxy, arylthio, aralkylthio, aryl and aralkyl groups having at least one substituent selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups amino

10 groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups,

or a pharmaceutically acceptable salt thereof.

3. A composition as claimed in Claim 2, wherein X represents a C<sub>1</sub>-C<sub>8</sub> alkylene group which is unsubstituted or has one or two substituents selected from: hydroxy groups; C<sub>1</sub>-C<sub>4</sub> alkoxy groups; aryloxy groups wherein the aryl ring has from 6 to 14 ring carbon atoms and which is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; C<sub>7</sub>-C<sub>8</sub> aralkyloxy groups, wherein the aryl moiety is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; mercapto groups; C<sub>1</sub>-C<sub>4</sub> alkylthio groups; arylthio groups wherein the aryl ring has from 6 to 14 ring carbon atoms and which is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; C<sub>7</sub>-C<sub>8</sub> aralkylthio groups wherein the aryl ring is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups;

carboxyalkylthio groups in which the alkyl part has from 1 to 4 carbon atoms; amino groups; amino groups having one or two C<sub>1</sub>-C<sub>4</sub> alkyl substituents; amino groups having one or two aryl substituents in which the aryl ring has from 6 to 14 ring carbon atoms and is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; amino groups having one or two C<sub>7</sub>-C<sub>8</sub> aralkyl substituents in which the aryl part is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; amino groups having one or two carboxylic acyl substituents; aryl groups having from 6 to 14 ring carbon atoms and being unsubstituted or having from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; carboxy groups; and heterocyclic groups having from 5 to 9 ring atoms, of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur hetero-atoms.

4. A composition as claimed in Claim 2, wherein X represents a C<sub>1</sub>-C<sub>8</sub> alkylene group which is unsubstituted or has 1 or 2 substituents selected from: hydroxy groups; C<sub>1</sub>-C<sub>4</sub> alkoxy groups; mercapto groups; C<sub>1</sub>-C<sub>4</sub> alkylthio groups; amino groups; amino groups having one or two C<sub>1</sub>-C<sub>4</sub> alkyl substituents; amino groups having one or two carboxylic acyl substituents; aryl groups having from 6 to 14 carbon atoms wherein the aryl ring is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; carboxy groups; and heterocyclic groups having from 5 to 9 ring atoms, of which from 1 to 3 are nitrogen and/or oxygen hetero-atoms.

40 5. A composition as claimed in any; one of Claims 1 to 4, wherein the N-acyl group is: a C<sub>1</sub>-C<sub>10</sub> alkanoyl group; a C<sub>2</sub>-C<sub>8</sub> alkenoyl group; a C<sub>2</sub>-C<sub>8</sub> alkynoyl group; an aromatic acyl group wherein the aryl part is C<sub>6</sub>-C<sub>10</sub> carbocyclic aryl and is unsubstituted or has from 1 to 5 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, C<sub>1</sub>-C<sub>4</sub> alkoxy groups, amino groups, sulpho groups and halogen atoms; a cycloalkanecarbonyl group where the cycloalkane part is C<sub>3</sub>-C<sub>8</sub> and is unsubstituted or has at least one substituent selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and phenyl groups; an araliphatic acyl group in which the aryl ring is a carbocyclic ring having from 6 to 14 carbon atoms and which is unsubstituted or has from 1 to 5 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, C<sub>1</sub>-C<sub>4</sub> alkoxy groups, amino groups, sulpho groups and halogen atoms, and in which the alkyl moiety has from 1 to 4 carbon atoms; a heterocyclic acyl group which has a saturated or unsaturated ring system, the rings having 5 or 6 ring atoms, of which from 1 to 3 are nitrogen and/or sulphur and/or oxygen hetero-atoms and the ring being unsubstituted or having from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and hydroxy groups; a C<sub>2</sub>-C<sub>8</sub> alkoxy carbonyl group; an aralkyloxy carbonyl group where the aralkyl part has from 7 to 9 carbon atoms and is unsubstituted or has from 1 to 5 substituents selected from amino groups, C<sub>1</sub>-C<sub>4</sub> alkyl groups, C<sub>1</sub>-C<sub>4</sub> alkoxy groups and hydroxy groups; or an acyl group derived from an amino acid by removal of OH from the carboxylic acid group and N-acylation of the amino group with at least one of the above-mentioned acyl groups.

6. A composition as claimed in any one of Claims 1 to 4, wherein the N-acyl group is: a saturated aliphatic acyl group having from 1 to 8 carbon atoms; an aromatic acyl group in which the aryl moiety has from 6 to 10 ring carbon atoms and is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; an alicyclic acyl group in which the cycloalkane ring has from 3 to 6 carbon atoms; an araliphatic acyl group in which the aryl ring has from 6 to 10 ring carbon atoms and the alkyl group has from 1 to 4 carbon atoms, the aryl ring being unsubstituted or having from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; a heterocyclic acyl group in which the heterocyclic ring is saturated or unsaturated and has 5 or 6 ring atoms of which one is a nitrogen, sulphur or oxygen hetero-atom; an alkoxycarbonyl group having a total of from 2 to 7 carbon atoms; an aralkyloxycarbonyl group in which the aralkyl moiety has from 7 to 9 carbon atoms and the aryl ring is unsubstituted or has from 1 to 3 substituents selected C<sub>1</sub>-C<sub>4</sub> alkyl groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; or an acyl group derived from an amino acid by removal of OH from the carboxylic acid group and N-acylation of the amino group with at least one of the above-mentioned acyl groups.

7. A composition as claimed in any; one of Claims 1 to 4, wherein the N-acyl group is: an aromatic acyl group in which the aryl ring has from 6 to 10 ring atoms and which is unsubstituted or has a single substituent selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, C<sub>1</sub>-C<sub>4</sub> alkoxy groups, hydroxy groups and amino groups; an alicyclic acyl group in which the cycloalkane moiety has from 3 to 6 carbon atoms; a phenylaliphatic acyl group in which the phenyl group is unsubstituted or has a single C<sub>1</sub>-C<sub>4</sub> alkyl substituent, and in which the alkyl part has from 1 to 4 carbon atoms; an alkoxycarbonyl group having a total of from 4 to 6 carbon atoms; an aralkyloxycarbonyl group in which the aralkyl part has from 7 to 9 carbon atoms and has 0 to 1 substituent selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; or an acyl group derived from an amino acid by removal of OH from the carboxylic acid group and N-acylation of the amino group with at least one of the above-mentioned acyl groups.

8. A composition as claimed in any one of Claims 1 to 4 wherein the N-acyl group is an acetyl, benzoyl, cyclohexanecarbonyl, cyclopropanecarbonyl, hexanoyl, isobutyryl, crotonoyl, ethoxycarbonyl, 4-hydroxybenzoyl, anisoyl, 4-aminobenzoyl, naphthoyl, toluoyl, benzyloxycarbonyl or 4-methoxybenzyloxycarbonyl group.

9. A composition as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is glycine,  $\beta$ -alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminoheptanoic acid, 8-aminooctanoic acid, alanine, 2-aminobutyric acid, norvaline valine, leucine, isoleucine, norleucine, tyrosine, Q-methyltyrosine, aspartic acid, glutamic acid, 4-carboxyglutamic acid, 3-methylaspartic acid, 2-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid, 3-hydroxyaspartic acid, 3-hydroxyglutamic acid, 2,3-diaminopropionic acid, 2,4-diaminobutyric acid, 5-hydroxylysine, arginine, N <sup>$\delta$</sup> , N <sup>$\delta$</sup> -dimethylornithine, N <sup>$\epsilon$</sup> -methyllysine, cysteine, methionine, ethionine, S-carboxymethylcysteine, S-benzylcysteine, methionine S-oxide, ethionine S-oxide, methionine S,S-dioxide, cysteic acid, serine, Q-methylserine, threonine, Q-methylthreonine, homothreonine, ethoxinine, 3-methoxyvaline, 3-phenylserine, 3-methyl-3-phenylalanine, histidine, tryptophan, 2-methylalanine, 2-methylserine, 2-hydroxyisoleucine, 2-methylmethionine, 2-ethyl-2-phenylglycine, 3-aminobutyric acid, 3-amino-4-methylvaleric acid, 3-amino-3-phenylpropionic acid, 3-amino-2-hydroxypropionic acid or 4-amino-3-hydroxybutyric acid.

10. A composition as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is glycine,  $\beta$ -alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminoheptanoic acid, 8-aminooctanoic acid, alanine, norvaline, valine, leucine, isoleucine, norleucine, N <sup>$\delta$</sup> , N <sup>$\delta$</sup> -dimethylornithine, methionine, ethionine, Q-methylserine, Q-methylthreonine, ethoxinine, 3-methoxyvaline, 3-phenylserine, 3-methyl-3-phenylalanine, histidine, 2-methylalanine, 2-methylserine, 2-hydroxyisoleucine, 2-ethylphenylglycine, 3-aminobutyric acid, 3-amino-4-methylvaleric acid or 3-amino-3-phenylpropionic acid.

11. A composition as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is  $\beta$ -alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminoheptanoic acid, alanine, valine, leucine, norleucine, methionine, histidine or glycine.

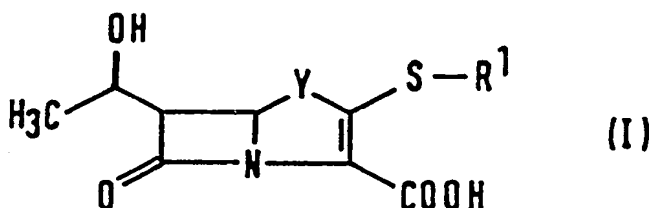
12. A composition as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is leucylglycine, glycyl- $\beta$ -alanine, glycylalanine, valylalanine, leucylalanine, glycylvaline, alanylvaline, leucylvaline, valylleucine, phenylalanylleucine, histidylleucine, glycylphenylalanine, alanylphenylalanine, leucylphenylalanine, glycylmethionine, valylmethionine, glycylhistidine, alanylvalylglycine, glycylalanylvaline, glycylphenylalanylleucine or glycylglycylhistidine.

13. A composition as claimed in Claim 1, wherein said N-acylated amino acid is:

- N-(p-toluoyl)- $\beta$ -alanine
- N-(4-methoxybenzoyl)- $\beta$ -alanine
- N-(3-hydroxy-2-naphthoyl)- $\beta$ -alanine
- N-benzoylglycyl- $\beta$ -alanine

- N-benzoyl- $\beta$ -alanine  
N-benzoyl-5-aminovaleric acid  
N-benzoyl-6-aminohexanoic acid  
N-cyclohexanecarbonyl-6-aminohexanoic acid  
5 N-(N-methylnicotinoyl)-6-aminohexanoic acid  
N-benzoyl-8-aminooctanoic acid  
N-benzoylalanine  
N-(1-naphthoyl)alanine  
N-benzoylvalylalanine  
10 N-benzoyl-2-aminobutyric acid  
N-benzoylnorvaline  
N-valerylvaline  
N-benzoylalanylvaline  
N-benzoylvaline  
15 N-benzoylleucine  
N-benzoylglycylphenylalanylleucine  
N-benzoylnorleucine  
N-benzoylglycylphenylalanine  
N-benzoylalanylphenylalanine  
20 N-cyclohexanecarbonylleucylphenylalanine  
N-benzoyl-Q-methyltyrosine  
N-benzoylmethionine  
N-phenylacetylmethionine  
N-benzoylvalylmethionine  
25 N-benzoylethionine  
N-(4-methoxybenzoyloxycarbonyl)ethionine  
N-benzoylthreonine  
N-benzoylhistidine  
N-(p-toluoyl)histidine  
30 N-(4-methoxybenzoyl)histidine  
N-(4-methoxybenzoyl)-3-aminobutyric acid  
or  
N-butyryl-3-amino-3-phenylpropionic acid.

14. A composition as claimed in any one of the preceding Claims, wherein said antibiotic is a compound of formula (I):



Y represents a sulphur atom, a methylene group or a methylene group having 1 or 2 methyl and/or methoxy substituents; and

R<sup>1</sup> represents a C<sub>1</sub>-C<sub>4</sub> alkyl group, a C<sub>1</sub>-C<sub>4</sub> alkyl group having at least one of substituents (i) or a heterocyclic group having from 4 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms where said heterocyclic group is unsubstituted or has at least one of substituents (ii);

substituents (i):  
 halogen atoms, amino groups, amino groups having at least one of substituents (iii), C<sub>1</sub>-C<sub>4</sub> alkylideneamino groups, C<sub>1</sub>-C<sub>4</sub> aminoalkylideneamino groups, amidino groups, amidino groups having from 1 to 3 of substituents (iii), heterocyclic groups having from 4 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms wherein said heterocyclic group is unsubstituted or has at least one of substituents (ii), imino groups, cyano groups, carbamoyl groups and carbamoyl groups having at least one substituent selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups;

substituents (ii):

- C<sub>1</sub>-C<sub>6</sub> alkanimidoyl groups, C<sub>1</sub>-C<sub>6</sub> alkyl groups, alkoxyalkyl groups where the alkoxy and alkyl parts are each C<sub>1</sub>-C<sub>4</sub>, carbamoyl groups, carbamoyl groups having at least one substituent selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups, C<sub>1</sub>-C<sub>6</sub> haloalkyl groups, heterocyclic acylimidoyl groups where the heterocyclic part has from 5 to 9 ring atoms of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur hetero-atoms, amidino groups, amidino groups having from 1 to 3 of substituents (iii), imino groups, oxygen atoms, C<sub>1</sub>-C<sub>6</sub> alkanoyl groups, C<sub>1</sub>-C<sub>6</sub> alkanesulphonyl groups, C<sub>1</sub>-C<sub>6</sub> alkanesulphonyl groups, hydroximino groups, C<sub>1</sub>-C<sub>6</sub> alkoximino groups, carbamoyloxy groups, carbamoyloxy groups having at least one substituent selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups, carbamoyloxyalkyl groups where the alkyl part is C<sub>1</sub>-C<sub>4</sub> and the carbamoyl part is unsubstituted or has at least one substituent selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups and C<sub>1</sub>-C<sub>4</sub> iminoalkyl groups;

substituents (iii):

- C<sub>1</sub>-C<sub>6</sub> alkyl groups, C<sub>2</sub>-C<sub>6</sub> alkenyl groups, C<sub>2</sub>-C<sub>6</sub> alkynyl groups, oxygen atoms and said alkyl, alkenyl and alkynyl groups having at least one substituent selected from halogen atoms, carbamoyloxy groups and carbamoyloxy groups having at least one substituent selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups;

and pharmaceutically acceptable salts thereof.

15. A composition as claimed in Claim 14, wherein Y represents a sulphur atom, a methylene group, or the group CH<sub>2</sub>-CH<, CH<sub>2</sub>O-CH< or (CH<sub>2</sub>)<sub>2</sub>C<.

- 20 16. A composition as claimed in Claim 14 or Claim 15, wherein R' represents an ethyl, 2-fluoroethyl, 2-(aminomethyleneamino)ethyl, N',N'-dimethylamidinomethyl, N', N', N'-trimethylamidinomethyl, 3-pyrrolidinyl, 1-formimidoyl-3-pyrrolidinyl, 1-acetimidoyl-3-pyrrolidinyl, 1-propionimidoyl-3-pyrrolidinyl, 2-methyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 2-methoxymethyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 3-azetidiny, 1-acetimidoyl-3-azetidiny, N'-methyl-N'-(2-propynyl)amidinomethyl, N'-(2-fluoroethyl)-N'-methylamidinomethyl, N'-(3-fluoropropyl)-N'-methylamidinomethyl, N'-methyl-N'-(2,2,2-trifluoroethyl)-amidinomethyl, 1-(3-azetidiny)ethyl, 1-(1-acetimidoyl-3-azetidiny)ethyl, 1,4,5,6-tetrahydro-2-pyrimidinyl-methyl, 1-(4,5-dihydro-2-thiazolyl)ethyl, 5-carbamoyl-3-pyrrolidinyl, 1-acetimidoyl-5-carbamoyl-3-pyrrolidinyl, 2-chloromethyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 1-butyrimidoyl-3-pyrrolidinyl, 1-nicotinimidoyl-3-pyrrolidinyl, N',N'-diallylamidinomethyl, N'-methyl-N'-(2-propynyl)amidino, N'-(2-fluoroethyl)-N'-methylamidino, N'-(3-fluoropropyl)-N'-methylamidino, N'-methyl-N'-(2,2,2-trifluoroethyl)amidino, N'-allyl-N'-methylamidinomethyl, cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 2-cyano-1-methylethyl, 2-aminoethyl, 1-carbamoylethyl, 2-(1-aminoethylideneamino)ethyl, 1-amidino-3-pyrrolidinyl, 2-methyl-1,3-diazabicyclo-[3.3.0]oct-2-en-7-yl, 2-methoxymethyl-1,3-diazabicyclo[3.3.0]oct-2-en-7-yl, 5-imino-2-pyrrolidinyl, 2-imino-5-piperidinyl, 1-acetimidoyl-5-methylcarbamoyl-3-pyrrolidinyl, 1-acetimidoyl-5-methoxycarbamoyl-3-pyrrolidinyl, 2-imino-2-(S-oxothiomorpholino)ethyl, 2-imino-2-(1,1-dioxo-1,3-thiazolidin-3-yl)ethyl, 2-imino-2-(S,S-dioxothiomorpholino)ethyl, 2-imino-2-(3,5-dioxo-1-piperazinyl)ethyl, 2-imino-2-(4-methyl-3,5-dioxo-1-piperazinyl)ethyl, 2-imino-2-(3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-methyl-3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-acetyl-3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-methanesulphonyl-3-oxo-1-piperazinyl)ethyl, N'-(2-carbamoyloxyethyl)-N'-methylamidinomethyl, 2-(3-hydroximino-1-pyrrolidinyl)2-iminoethyl, 2-imino-2-(3-methoximino-1-pyrrolidinyl)-ethyl, 2-(4-hydroximino-piperidino)-2-iminoethyl, 2-imino-2-(4-methoximino-piperidino)ethyl, 2-(3-carbamoyloxy-1-pyrrolidinyl)-2-iminoethyl, 2-imino-2-(3-oxo-1-piperazinyl)ethyl, 2-(3-carbamoylpiperidino)-2-iminoethyl, 2-(3-carbamoyloxypiperidino)-2-iminoethyl, 2-(2-carbamoyloxy-1-pyrrolidinyl)-2-iminoethyl, 2-(2-carbamoyloxymethyl-1-pyrrolidinyl)-2-iminoethyl, 2-(4-carbamoyloxypiperidino)-2-iminoethyl, 2-(4-formyl-1-piperazinyl)-2-iminoethyl, 2-(4-acetyl-1-piperazinyl)-2-iminoethyl, 1-formyl-3-azetidiny, 1-iminomethyl-3-azetidiny, 1-methyl-4-piperidyl, 1-acetimidoyl-4-piperidyl or 1-acetyl-3-pyrrolidinyl group.

17. A composition as claimed in Claim 14, wherein said antibiotic is:

- (5R,6S)-2-{2-[(aminomethylene)amino]ethylthio}-6-[1(R)-hydroxyethyl]-2-carbapenam-3-carboxylic acid  
 (5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenam-3-carboxylic acid  
 (5R,6S)-2-[(3R)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenam-3-carboxylic acid  
 50 (5R,6S)-2-[(3R)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(S)-methyl-2-carbapenam-3-carboxylic acid  
 (5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(R)-methyl-2-carbapenam-3-carboxylic acid  
 (5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(S)-methyl-2-carbapenam-3-carboxylic acid  
 55 or  
 (5R,6S)-2-[(3S)-1-acetimidoyl-5(S)-carbamoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenam-3-carboxylic acid.

18. A composition as claimed in any one of the preceding Claims, wherein the weight ratio of said N-acylated amino acid to said antibiotic is from 0.1:1 to 4:1.

19. A packaged pharmaceutical preparation comprising:

(a) in one part, a penem or carbapenem antibiotic; and

5 (b) in another part, a pharmaceutically acceptable N-acylated derivative of an amino acid wherein the amino group and the carboxylic acid group are attached to a saturated aliphatic carbon chain or carbon atom, or a salt thereof, provided that the amino acid is not ornithine, lysine, phenylalanine or phenylglycine alone.

20. A preparation as claimed in Claim 19, wherein said N-acylated amino acid is as defined in any one of Claims 2 to 13.

21. A preparation as claimed in Claim 19 or Claim 20, wherein said antibiotic is as defined in any one of Claims 14 to 17.

22. The use for the manufacture of a medicament for the treatment of bacterial infections of:

(a) a penem or carbapenem antibiotic;

15 in association with:

(b) a pharmaceutically acceptable N-acylated derivative of an amino acid wherein the amino group and the carboxylic acid group are attached to a saturated aliphatic carbon chain or carbon atom, or a salt thereof, provided that the amino acid is not ornithine, lysine, phenylalanine or phenylglycine alone.

23. The use as claimed in Claim 22, wherein said N-acylated amino acid is as defined in any one of Claims 2 to 13.

24. The use as claimed in Claim 22 or Claim 23, wherein said antibiotic is as defined in any one of Claims 14 to 17.

Claims for the following Contracting States : AT, ES:

25

1. A method of making a pharmaceutical composition by mixing:

a penem or carbapenem antibiotic; and

a pharmaceutically acceptable N-acylated derivative of an amino acid wherein the amino group and the carboxylic acid group are attached to a saturated aliphatic carbon chain or carbon atom, or a salt thereof, provided that the amino acid is not ornithine, lysine, phenylalanine or phenylglycine alone.

30

2. A method as claimed in Claim 1, wherein said amino acid is a compound of formula (II):

$H_2N-X-COOH$  (II)

wherein X represents a  $C_1-C_{10}$  alkylene group or a  $C_1-C_{10}$  alkylene group having at least one substituent selected from hydroxy groups,  $C_1-C_4$  alkoxy groups,  $C_6-C_{10}$  aryloxy groups, substituted  $C_6-C_{10}$  aryloxy groups,  $C_7-C_8$  aralkyloxy groups, substituted  $C_7-C_8$  aralkyloxy groups, mercapto groups,  $C_1-C_4$  alkylthio groups,  $C_6-C_{10}$  arylthio groups, substituted  $C_6-C_{10}$  arylthio groups,  $C_7-C_8$  aralkylthio groups, substituted  $C_7-C_8$  aralkylthio groups,  $C_2-C_3$  carboxyalkylthio groups, amino groups, amino groups having one or two substituents selected from

35

$C_1-C_4$  alkyl groups,  $C_6-C_{10}$  aryl groups, substituted  $C_6-C_{10}$  aryl groups,  $C_7-C_8$  aralkyl groups, substituted  $C_7-C_8$  aralkyl groups and carboxylic acyl groups,

40

$C_6-C_{10}$  aryl groups, substituted  $C_6-C_{10}$  aryl groups, carboxy groups, amidino groups, sulpho groups,  $C_1-C_4$  alkylsulphinyl groups,  $C_1-C_4$  alkylsulphonyl groups and heterocyclic groups having from 5 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms, said substituted aryloxy, aralkyloxy, arylthio, aralkylthio, aryl and aralkyl groups having at least one substituent selected from  $C_1-C_4$  alkyl groups, hydroxy groups, amino groups and  $C_1-C_4$  alkoxy groups,

45

or a pharmaceutically acceptable salt thereof.

3. A method as claimed in Claim 2, wherein X represents a  $C_1-C_8$  alkylene group which is unsubstituted or has one or two substituents selected from: hydroxy groups;  $C_1-C_4$  alkoxy groups; aryloxy groups wherein the aryl ring has from 6 to 14 ring carbon atoms and which is unsubstituted or has from 1 to 3 substituents selected from  $C_1-C_4$  alkyl groups, hydroxy groups, amino groups and  $C_1-C_4$  alkoxy groups;  $C_7-C_8$  aralkyloxy groups, wherein the aryl moiety is unsubstituted or has from 1 to 3 substituents selected from  $C_1-C_4$  alkyl groups, hydroxy groups, amino groups and  $C_1-C_4$  alkoxy groups; mercapto groups;  $C_1-C_4$  alkylthio groups; arylthio groups wherein the aryl ring has from 6 to 14 ring carbon atoms and which is unsubstituted or has from 1 to 3 substituents selected from  $C_1-C_4$  alkyl groups, hydroxy groups, amino groups and  $C_1-C_4$  alkoxy groups;  $C_7-C_8$  aralkylthio groups wherein the aryl ring is unsubstituted or has from 1 to 3 substituents selected from  $C_1-C_4$  alkyl groups, hydroxy groups, amino groups and  $C_1-C_4$  alkoxy groups; carboxyalkylthio groups in which the alkyl part has from 1 to 4 carbon atoms; amino groups; amino groups having one or two  $C_1-C_4$  alkyl substituents; amino groups having one or two aryl substituents in which the aryl ring has

50

55

from 6 to 14 ring carbon atoms and is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; amino groups having one or two C<sub>1</sub>-C<sub>4</sub> aralkyl substituents in which the aryl part is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; amino groups having one or two carboxylic acyl substituents; aryl groups having from 6 to 14 ring carbon atoms and being unsubstituted or having from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; carboxy groups; and heterocyclic groups having from 5 to 9 ring atoms, of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur hetero-atoms.

4. A method as claimed in Claim 2, wherein X represents a C<sub>1</sub>-C<sub>4</sub> alkylene group which is unsubstituted or has 1 or 2 substituents selected from: hydroxy groups; C<sub>1</sub>-C<sub>4</sub> alkoxy groups; mercapto groups; C<sub>1</sub>-C<sub>4</sub> alkylthio groups; amino groups; amino groups having one or two C<sub>1</sub>-C<sub>4</sub> alkyl substituents; amino groups having one or two carboxylic acyl substituents; aryl groups having from 6 to 14 carbon atoms wherein the aryl ring is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, amino groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; carboxy groups; and heterocyclic groups having from 5 to 9 ring atoms, of which from 1 to 3 are nitrogen and/or oxygen hetero-atoms.

5. A method as claimed in any one of Claims 1 to 4, wherein the N-acyl group is: a C<sub>1</sub>-C<sub>18</sub> alkanoyl group; a C<sub>2</sub>-C<sub>18</sub> alkenoyl group; a C<sub>2</sub>-C<sub>18</sub> alkynoyl group; an aromatic acyl group wherein the aryl part is C<sub>6</sub>-C<sub>14</sub> carbocyclic aryl and is unsubstituted or has from 1 to 5 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, C<sub>1</sub>-C<sub>4</sub> alkoxy groups, amino groups, sulpho groups and halogen atoms; a cycloalkanecarbonyl group where the cycloalkane part is C<sub>3</sub>-C<sub>8</sub> and is unsubstituted or has at least one substituent selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and phenyl groups; an araliphatic acyl group in which the aryl ring is a carbocyclic ring having from 6 to 14 carbon atoms and which is unsubstituted or has from 1 to 5 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, hydroxy groups, C<sub>1</sub>-C<sub>4</sub> alkoxy groups, amino groups, sulpho groups and halogen atoms, and in which the alkyl moiety has from 1 to 4 carbon atoms; a heterocyclic acyl group which has a saturated or unsaturated ring system, the rings having 5 or 6 ring atoms, of which from 1 to 3 are nitrogen and/or sulphur and/or oxygen hetero-atoms and the ring being unsubstituted or having from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and hydroxy groups; a C<sub>2</sub>-C<sub>7</sub> alkoxycarbonyl groups; an aralkyloxycarbonyl group where the aralkyl part has from 7 to 9 carbon atoms and is unsubstituted or has from 1 to 5 substituents selected from amino groups, C<sub>1</sub>-C<sub>4</sub> alkyl groups, C<sub>1</sub>-C<sub>4</sub> alkoxy groups and hydroxy groups; or an acyl group derived from an amino acid by removal of OH from the carboxylic acid group and N-acylation of the amino group with at least one of the above-mentioned acyl groups.

6. A method as claimed in any one of Claims 1 to 4, wherein the N-acyl group is: a saturated aliphatic acyl group having from 1 to 8 carbon atoms; an aromatic acyl group in which the aryl moiety has from 6 to 10 ring carbon atoms and is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; an alicyclic acyl group in which the cycloalkane ring has from 3 to 6 carbon atoms; an araliphatic acyl group in which the aryl ring has from 6 to 10 ring carbon atoms and the alkyl group has from 1 to 4 carbon atoms, the aryl ring being unsubstituted or having from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; a heterocyclic acyl group in which the heterocyclic ring is saturated or unsaturated and has 5 or 6 ring atoms of which one is a nitrogen, sulphur or oxygen hetero-atom; an alkoxycarbonyl group having a total of from 2 to 7 carbon atoms; an aralkyloxycarbonyl group in which the aralkyl moiety has from 7 to 9 carbon atoms and the aryl ring is unsubstituted or has from 1 to 3 substituents selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; or an acyl group derived from an amino acid by removal of OH from the carboxylic acid group and N-acylation of the amino group with at least one of the above-mentioned acyl groups.

7. A method as claimed in any one of Claims 1 to 4, wherein the N-acyl group is: an aromatic acyl group in which the aryl ring has from 6 to 10 ring atoms and which is unsubstituted or has a single substituent selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups, C<sub>1</sub>-C<sub>4</sub> alkoxy groups, hydroxy groups and amino groups; an alicyclic acyl group in which the cycloalkane moiety has from 3 to 6 carbon atoms; a phenylaliphatic acyl group in which the phenyl group is unsubstituted or has a single C<sub>1</sub>-C<sub>4</sub> alkyl substituent, and in which the alkyl part has from 1 to 4 carbon atoms; an alkoxycarbonyl group having a total of from 4 to 6 carbon atoms; an aralkyloxycarbonyl group in which the aralkyl part has from 7 to 9 carbon atoms and has 0 or 1 substituent selected from C<sub>1</sub>-C<sub>4</sub> alkyl groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups; or an acyl group derived from an amino acid by removal of OH from the carboxylic acid group and N-acylation of the amino group with at least one of the above-mentioned acyl groups.

8. A method as claimed in any one of Claims 1 to 4, wherein the N-acyl group is an acetyl, benzoyl, cyclohexanecarbonyl, cyclopropanecarbonyl, hexanoyl, isobutyryl, crotonoyl ethoxycarbonyl, 4-hydroxybenzoyl, anisoyl, 4-aminobenzoyl, naphthoyl, toluoyl, benzyloxycarbonyl or 4-methoxybenzyloxycarbonyl group.

9. A method as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is glycine,  $\beta$ -alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, 8-aminooctanoic acid, alanine, 2-aminobutyric acid, norvaline, valine, leucine, isoleucine, norleucine, tyrosine, Q-methyltyrosine, aspartic acid, glutamic acid, 4-carboxyglutamic acid, 3-methylaspartic acid, 2-aminoadipic acid, 2-aminopimelic acid, 5 2-aminosuberic acid, 3-hydroxyaspartic acid, 3-hydroxyglutamic acid, 2,3-diaminopropionic acid, 2,4-diaminobutyric acid, 5-hydroxylysine, arginine, N<sup>5</sup>,N<sup>6</sup>-dimethylhomithine, N<sup>6</sup>-methyllysine, cysteine, methionine, ethionine, S-carboxymethylcysteine, S-benzylcysteine, methionine S-oxide, ethionine S-oxide, methionine S,S-dioxide, cysteic acid, serine, Q-methylserine, threonine, Q-methylthreonine, homothreonine, ethoxinine, 3-methoxyvaline, 3-phenylserine, 3-methyl-3-phenylalanine, histidine, tryptophan, 2- 10 methylalanine, 2-methylserine, 2-hydroxyisoleucine, 2-methylmethionine, 2-ethyl-2-phenylglycine, 3-aminobutyric acid, 3-amino-4-methylvaleric acid, 3-amino-3-phenylpropionic acid, 3-amino-2-hydroxypropionic acid or 4-amino-3-hydroxybutyric acid.

10. A method as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is glycine,  $\beta$ -alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, 8-aminooctanoic acid, alanine, norvaline, valine, leucine, isoleucine, norleucine, N<sup>5</sup>,N<sup>6</sup>-dimethylornithine, methionine, ethionine, Q-methylserine, Q-methylthreonine, ethoxinine, 3-methoxyvaline, 3-phenylserine, 3-methyl-3-phenylalanine, histidine, 2-methylalanine, 2-methylserine, 2-hydroxyisoleucine, 2-ethylphenylglycine, 3-aminobutyric acid, 3-amino-4-methylvaleric acid or 3-amino-3-phenylpropionic acid.

11. A method as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is  $\beta$ -alanine, 4-aminobutyric acid, 5-aminovaleric acid, 6-aminohexanoic acid, alanine, valine, leucine, norleucine, methionine, histidine or glycine.

12. A method as claimed in any one of Claims 1 and 5 to 8, wherein said amino acid is leucylglycine, glycyl- $\beta$ -alanine, glycylalanine, valylalanine, leucylalanine, glycylvaline, alanylvaline, leucylvaline, valyl- 25 leucine, phenylalanylleucine, histidylleucine, glycylphenylalanine, alanylphenylalanine, leucylphenylalanine, glycylmethionine, valylmethionine, glycylhistidine, alanylvalylglycine, glycylalanylvaline, glycylphenylalanyl-leucine or glycylglycylhistidine.

13. A method as claimed in Claim 1, wherein said N-acylated amino acid is:

- N-(p-toluoyl)- $\beta$ -alanine
- 30 N-(4-methoxybenzoyl)- $\beta$ -alanine
- N-(3-hydroxy-2-naphthoyl)- $\beta$ -alanine
- N-benzoylglycyl- $\beta$ -alanine
- N-benzoyl- $\beta$ -alanine
- N-benzoyl-5-aminovaleric acid
- 35 N-benzoyl-6-aminohexanoic acid
- N-cyclohexanecarbonyl-6-aminohexanoic acid
- N-(N-methylnicotinoyl)-6-aminohexanoic acid
- N-benzoyl-8-aminooctanoic acid
- N-benzoylalanine
- 40 N-(1-naphthoyl)alanine
- N-benzoylvalylalanine
- N-benzoyl-2-aminobutyric acid
- N-benzoylnorvaline
- N-valerylvaline
- 45 N-benzoylalanylvaline
- N-benzoylvaline
- N-benzoylleucine
- N-benzoylglycylphenylalanylleucine
- N-benzoylnorleucine
- 50 N-benzoylglycylphenylalanine
- N-benzoylalanylphenylalanine
- N-cyclohexanecarbonylleucylphenylalanine
- N-benzoyl-Q-methyltyrosine
- N-benzoylmethionine
- 55 N-phenylacetylmethionine
- N-benzoylvalylmethionine
- N-benzoylethionine
- N-(4-methoxybenzyloxycarbonyl)ethionine

N-benzoylthreonine

N-benzoylhistidine

N-(*p*-toluoyl)histidine

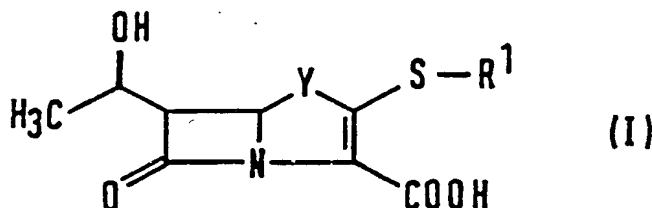
N-(4-methoxybenzoyl)histidine

5 N-(4-methoxybenzoyl)-3-aminobutyric acid

or

N-butyryl-3-amino-3-phenylpropionic acid.

14. A method as claimed in any one of the preceding Claims, wherein said antibiotic is a compound of formula (I):



in which:

Y represents a sulphur atom, a methylene group or a methylene group having 1 or 2 methyl and/or methoxy substituents; and

25 R<sup>1</sup> represents a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> alkyl group having at least one of substituents (i) or a heterocyclic group having from 4 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms where said heterocyclic group is unsubstituted or has at least one of substituents (ii);

substituents (i):  
halogen atoms, amino groups, amino groups having at least one of substituents (iii), C<sub>1</sub>-C<sub>6</sub> alkylideneamino groups, C<sub>1</sub>-C<sub>6</sub> aminoalkylideneamino groups, amidino groups, amidino groups having from 1 to 3 of substituents (iii), heterocyclic groups having from 4 to 14 ring atoms of which from 1 to 5 are nitrogen and/or oxygen and/or sulphur hetero-atoms wherein said heterocyclic group is unsubstituted or has at least one of substituents (ii), imino groups, cyano groups, carbamoyl groups and carbamoyl groups having at least one substituent selected from C<sub>1</sub>-C<sub>6</sub> alkyl groups and C<sub>1</sub>-C<sub>6</sub> alkoxy groups;

substituents (ii):  
35 C<sub>1</sub>-C<sub>6</sub> alkanimidoyl groups, C<sub>1</sub>-C<sub>6</sub> alkyl groups, alkoxyalkyl groups where the alkoxy and alkyl parts are each C<sub>1</sub>-C<sub>6</sub>, carbamoyl groups, carbamoyl groups having at least one substituent selected from C<sub>1</sub>-C<sub>6</sub> alkyl groups and C<sub>1</sub>-C<sub>6</sub> alkoxy groups, C<sub>1</sub>-C<sub>6</sub> haloalkyl groups, heterocyclic acylimidoyl groups where the heterocyclic part has from 5 to 9 ring atoms of which from 1 to 3 are nitrogen and/or oxygen and/or sulphur hetero-atoms, amidino groups, amidino groups having from 1 to 3 of substituents (iii), amino groups, oxygen atoms, C<sub>1</sub>-C<sub>6</sub> alkanoyl groups, C<sub>1</sub>-C<sub>6</sub> alkanesulphonyl groups, C<sub>1</sub>-C<sub>6</sub> alkanesulphonyl groups, hydroximino groups, C<sub>1</sub>-C<sub>6</sub> alkoximino groups, carbamoyloxy groups, carbamoyloxy groups having at least one substituent selected from C<sub>1</sub>-C<sub>6</sub> alkyl groups and C<sub>1</sub>-C<sub>6</sub> alkoxy groups, carbamoyloxyalkyl groups where the alkyl part is C<sub>1</sub>-C<sub>6</sub> and the carbamoyl part is unsubstituted or has at least one substituent selected from C<sub>1</sub>-C<sub>6</sub> alkyl groups and C<sub>1</sub>-C<sub>6</sub> alkoxy groups and C<sub>1</sub>-C<sub>6</sub> iminoalkyl groups;

substituents (iii):  
45 C<sub>1</sub>-C<sub>6</sub> alkyl groups, C<sub>2</sub>-C<sub>6</sub> alkenyl groups, C<sub>2</sub>-C<sub>6</sub> alkynyl groups, oxygen atoms and said alkyl, alkenyl and alkynyl groups having at least one substituent selected from halogen atoms, carbamoyloxy groups and carbamoyloxy groups having at least one substituent selected from C<sub>1</sub>-C<sub>6</sub> alkyl groups and C<sub>1</sub>-C<sub>6</sub> alkoxy groups;

50 and pharmaceutically acceptable salts thereof.

15. A method as claimed in Claim 14, wherein Y represents a sulphur atom, a methylene group, or the group CH<sub>2</sub>-CH<, CH<sub>2</sub>O-CH< or (CH<sub>2</sub>)<sub>2</sub>C<.

16. A method as claimed in Claim 14 or Claim 15, wherein R<sub>1</sub> represents an ethyl, 2-fluoroethyl, 2-(aminomethyleneamino)ethyl, N<sup>1</sup>,N<sup>1</sup>-dimethylamidinomethyl, N<sup>1</sup>,N<sup>1</sup>,N<sup>2</sup>-trimethylamidinomethyl, 3-pyrrolidinyl, 1-formimidoyl-3-pyrrolidinyl, 1-acetimidoyl-3-pyrrolidinyl, 1-propionimidoyl-3-pyrrolidinyl, 2-methyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 2-methoxymethyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 3-azetidyl, 1-acetimidoyl-3-azetidyl, N<sup>1</sup>-methyl-N<sup>1</sup>-(2-propynyl)amidinomethyl, N<sup>1</sup>-(2-fluoroethyl)-N<sup>1</sup>-methylamidinomethyl, N<sup>1</sup>-(3-fluoropropyl)-N<sup>1</sup>-methylamidinomethyl, N<sup>1</sup>-methyl-N<sup>1</sup>-(2,2,2-trifluoroethyl)amidinomethyl, 1-(3-azetidyl)ethyl,



1-(1-acetimidoyl-3-azetidinyl)ethyl, 1,4,5,6-tetrahydro-2-pyrimidinylmethyl, 1-(4,5-dihydro-2-thiazolyl)ethyl, 5-carbamoyl-3-pyrrolidinyl, 1-acetimidoyl-5-carbamoyl-3-pyrrolidinyl, 2-chloromethyl-1,4,5,6-tetrahydro-5-pyrimidinyl, 1-butyrimidoyl-3-pyrrolidinyl, 1-nicotinimidoyl-3-pyrrolidinyl, N<sup>1</sup>,N<sup>1</sup>-diallylamidinomethyl, N<sup>1</sup>-methyl-N<sup>1</sup>-(2-propynyl)amidino, N<sup>1</sup>-(2-fluoroethyl)-N<sup>1</sup>-methylamidino, N<sup>1</sup>-(3-fluoropropyl)-N<sup>1</sup>-methylamidino, 5 N<sup>1</sup>-methyl-N<sup>1</sup>-(2,2,2-trifluoroethyl)amidino, N<sup>1</sup>-allyl-N<sup>1</sup>-methylamidinomethyl, cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 2-cyano-1-methylethyl, 2-aminoethyl, 1-carbamoylethyl, 2-(1-aminoethylideneamino)ethyl, 1-amidino-3-pyrrolidinyl, 2-methyl-1-3-diazabicyclo-[3.3.0]oct-2-en-7-yl, 2-methoxymethyl-1,3-diazabicyclo-[3.3.0]oct-2-en-7-yl, 5-imino-2-pyrrolidinyl, 2-imino-5-piperidinyl, 1-acetimidoyl-5-methylcarbamoyl-3-pyrrolidinyl, 1-acetimidoyl-5-methoxycarbamoyl-3-pyrrolidinyl, 2-imino-2-(S-oxothiomorpholino)ethyl, 2-imino-2-10 (1,1-dioxo-1,3-thiazolidin-3-yl)ethyl, 2-imino-2-(S,S-dioxothiomorpholino)ethyl, 2-imino-2-(3,5-dioxo-1-piperazinyl)ethyl, 2-imino-2-(4-methyl-3,5-dioxo-1-piperazinyl)ethyl, 2-imino-2-(3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-methyl-3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-acetyl-3-oxo-1-piperazinyl)ethyl, 2-imino-2-(4-methanesulphonyl-3-oxo-1-piperazinyl)ethyl, N<sup>1</sup>-(2-carbamoyloxyethyl)N<sup>1</sup>-methylamidinomethyl, 2-(3-hydroximino-1-pyrrolidinyl)-2-iminoethyl, 2-imino-2-(3-methoximino-1-pyrrolidinyl)ethyl, 2-(4-hydroximinopiperidino)-2-iminoethyl, 2-imino-2-(4-methoximinopiperidino)ethyl, 2-(3-carbamoyloxy-1-pyrrolidinyl)-2-iminoethyl, 2-imino-2-(3-oxo-1-piperazinyl)ethyl, 2-(3-carbamoylpiperidino)-2-iminoethyl, 2-(3-carbamoyloxypiperidino)-2-iminoethyl, 2-(2-carbamoyloxy-1-pyrrolidinyl)-2-iminoethyl, 2-(2-carbamoyloxymethyl-1-pyrrolidinyl)-2-iminoethyl, 2-(4-carbamoyloxypiperidino)-2-iminoethyl, 2-(4-formyl-1-piperazinyl)-2-iminoethyl, 2-(4-acetyl-1-piperazinyl)-2-iminoethyl, 1-formyl-3-azetidinyl, 1-iminomethyl-3-azetidinyl, 1-methyl-4-piperidyl, 20 1-acetimidoyl-4-piperidyl or 1-acetyl-3-pyrrolidinyl group.

17. A method as claimed in Claim 14, wherein said antibiotic is:

(5*R*,6*S*)-2-{2-[(aminomethylene)amino]ethylthio}-6-[1(*R*)-hydroxyethyl]-2-carbapenem-3-carboxylic acid  
 (5*R*,6*S*)-2-{(3*S*)-1-acetimidoylpyrrolidin-3-ylthio}-6-[1(*R*)-hydroxyethyl]-2-carbapenem-3-carboxylic acid  
 (5*R*,6*S*)-2-{(3*R*)-1-acetimidoylpyrrolidin-3-ylthio}-6-[1(*R*)-hydroxyethyl]-2-carbapenem-3-carboxylic acid  
 25 (5*R*,6*S*)-2-{(3*R*)-1-acetimidoylpyrrolidin-3-ylthio}-6-[1(*R*)-hydroxyethyl]-1(*S*)-methyl-2-carbapenem-3-carboxylic acid  
 (5*R*,6*S*)-2-{(3*S*)-1-acetimidoylpyrrolidin-3-ylthio}-6-[1(*R*)-hydroxyethyl]-1(*R*)-methyl-2-carbapenem-3-carboxylic acid  
 (5*R*,6*S*)-2-{(3*S*)-1-acetimidoylpyrrolidin-3-ylthio}-6-[1(*R*)-hydroxyethyl]-1(*S*)-methyl-2-carbapenem-3-carboxylic acid  
 30 or (5*R*,6*S*)-2-{(3*S*)-1-acetimidoyl-5(*S*)-carbamoylpyrrolidin-3-ylthio}-6-[1(*R*)-hydroxyethyl]-2-carbapenem-3-carboxylic acid.

18. A method as claimed in any one of the preceding Claims, wherein the weight ratio of said N-acylated amino acid to said antibiotic is from 1:1 to 4:1.

35 19. A method according to any one of the preceding Claims, which comprises: solubilizing said N-acylated amino acid in water; adding and dissolving said antibiotic in the resulting; and optionally lyophilizing the solution to provide a powdery mixture.

20. A method according to Claim 19, in which said N-acylated amino acid is solubilized by dispersing it in water and adding sufficient of a base to adjust the pH to a value of from 5.5 to 9.

40 21. The use for the manufacture of a medicament for the treatment of bacterial infections of:

(a) a penem or carbapenem antibiotic;

in association with:

(b) a pharmaceutically acceptable N-acylated derivative of an amino acid wherein the amino group and the carboxylic acid group are attached to a saturated aliphatic carbon chain or carbon atom, or a salt thereof, provided that the amino acid is not ornithine, lysine, phenylalanine or phenylglycine alone.

22. The use as claimed in Claim 21, wherein said N-acylated amino acid is:

N-(*p*-toluoyl)- $\beta$ -alanine  
N-(4-methoxybenzoyl)- $\beta$ -alanine  
N-(3-hydroxy-2-naphthoyl)- $\beta$ -alanine  
 50 N-benzoylglycyl- $\beta$ -alanine  
N-benzoyl- $\beta$ -alanine  
N-benzoyl-5-aminovaleric acid  
N-benzoyl-6-aminoheptanoic acid  
N-cyclohexanecarbonyl-6-aminoheptanoic acid  
 55 N-(N-methylnicotinoyl)-6-aminoheptanoic acid  
N-benzoyl-8-aminooctanoic acid  
N-benzoylalanine  
N-(1-naphthoyl)alanine

- N-benzoylvalylalanine  
N-benzoyl-2-aminobutyric acid  
N-benzoylnorvaline  
N-valerylvaline  
5 N-benzoylalanylvaline  
N-benzoylvaline  
N-benzoylleucine  
N-benzoylglycylphenylalanylleucine  
N-benzoylnorleucine  
10 N-benzoylglycylphenylalanine  
N-benzoylalanylphenylalanine  
N-cyclohexanecarbonylleucylphenylalanine  
N-benzoyl-Q-methyltyrosine  
N-benzoylmethionine  
15 N-phenylacetylmethionine  
N-benzoylvalylmethionine  
N-benzoylethionine  
N-(4-methoxybenzyloxycarbonyl)ethionine  
N-benzoylthreonine  
20 N-benzoylhistidine  
N-(p-toluoyl)histidine  
N-(4-methoxybenzoyl)histidine  
N-(4-methoxybenzoyl)-3-aminobutyric acid  
or  
25 N-butyryl-3-amino-3-phenylpropionic acid.

23. The use as claimed in Claim 21 or Claim 22, wherein said antibiotic is:

- (5R,6S)-2-{2-[(aminomethylene)amino]ethylthio}-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid  
(5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid  
(5R,6S)-2-[(3R)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid  
30 (5R,6S)-2-[(3R)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(S)-methyl-2-carbapenem-3-carboxylic acid  
(5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(R)-methyl-2-carbapenem-3-carboxylic acid  
(5R,6S)-2-[(3S)-1-acetimidoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-1(S)-methyl-2-carbapenem-3-carboxylic acid  
35 ylic acid  
or  
(5R,6S)-2-[(3S)-1-acetimidoyl-5(S)-carbamoylpyrrolidin-3-ylthio]-6-[1(R)-hydroxyethyl]-2-carbapenem-3-carboxylic acid.

40

45

50

55



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application number

EP 86 30 8321

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP-A-0 048 301 (MERCK) * Page 3; claims *	1,2,14	A 61 K 31/40 A 61 K 31/43 // (A 61 K 31/40 A 61 K 31:195) (A 61 K 31/43 A 61 K 31:195)
A	EP-A-0 091 594 (SANRAKU-OCEAN CO.) * Claims *	1,2,14	
P,A D	EP-A-0 178 911 (SANKYO) * Claims *	1-24	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			A 61 K 31/00 C 07 D 487/00 C 07 D 499/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 14-01-1987	Examiner CHOULY J.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons  A : member of the same patent family, corresponding document	